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Title of Dissertation: "Social Support, Heart Failure, and Acute Coronary Syndromes: The Role of Inflammatory Markers"

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Doctor of Philosophy Degree
3 April 2008

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Abstract

Title of Thesis: "Social Support, Acute Coronary Syndromes, and Heart Failure: The Role of Inflammatory Processes"

Author: Heather L. Rogers, Doctor of Philosophy, 2008

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Heart failure (HF) is a growing clinical and public health problem associated with high morbidity and mortality. Structural and functional social support are implicated in the development and progression of cardiovascular disease (CVD), but not studied as a predictor of incident HF, and the bio-behavioral mechanisms that may underlie this relationship have not been examined. Inflammation, given its role in CVD and HF, may be one promising pathway. Study I used data from the Cardiovascular Health Study (CHS) to prospectively determine the value of structural vs. functional social support as a predictor of incident HF and the mediating role of inflammatory markers Interleukin-6 (IL-6) and C-reactive protein (CRP). Study II examined the relationship between specific types of structural and functional social support and inflammatory markers IL-6, CRP, and tumor necrosis factor–alpha (TNF-α) in a group of patients hospitalized with an acute coronary syndrome.

Study I results: Lack of social integration (a structural social support measure), but not functional social support, predicted incident HF in the CHS sample. Gender-specific analyses found this relationship in community-dwelling elderly males, but not females [HR=1.60(1.24–

2.08) for lowest vs. highest quartiles, p<0.001], independent of age, race/ethnicity, coronary disease, hypertension, diabetes, body mass index, and smoking. In males, social integration was related to IL-6 (r=-0.05, $p < 0.05$), but not CRP. However, IL-6 did not mediate the relationship between social integration and HF. Study *II results*: Tangible, appraisal, and belonging measures of functional social support were associated with number of hours visited (r's=0.32–0.44, p<0.05). Marital status was the strongest relative predictor of TNF-α (p<0.01), belonging of CRP (r=-0.32, p<0.05), and number of people in household significantly predicted IL-6 in this sample, above and beyond tangible social support and marital status, which were significantly related to IL-6 in univariate analyses ($p < 0.05$).

Study I and Study II findings partially confirm the conceptual model, suggesting that inflammation may be one pathway through which structural and functional social support influence health outcomes, but evidence does not favor an inflammatory pathway to explain the impact of social integration on incident HF in elderly males.

Social Support, Acute Coronary Syndromes, and Heart Failure:

The Role of Inflammatory Processes

by

Heather L. Rogers

Doctoral Dissertation submitted to the Faculty of the

Department of Medical and Clinical Psychology

Graduate Program of the Uniformed Services University

of the Health Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy, 2008

Acknowledgements

I am indebted to my mentor, David Krantz, Ph.D., for providing me with the guidance and training necessary to conceptualize and complete this work. He is a true scientist and I am forever grateful for his wisdom, inquisitiveness, constructive criticism, and support.

I am further indebted to my dissertation committee, Tracy Sbrocco, Ph.D. (chair), Mark Haigney, M.D., Marjan Holloway, Ph.D., and Gayle Page, D.N.Sc., R.N., for the diverse perspectives they contributed to this endeavor and their personal investment in my growth as a multi-disciplinary bio-behavioral researcher.

Former/current USUHS faculty members Willem Kop, Ph.D., Col. Robert Lipnick, Sc.D., Cara Olsen, M.S., and Richard Palmer, Dr.P.H. deserve special appreciation for their advice regarding the design and analysis of Study I.

Study II would not have been possible without the collaboration of the Johns Hopkins Center for Mind-Body Research faculty members Roy Ziegelstein, M.D., Marlene Williams, M.D., James Fauerbach, Ph.D., and Gina Magyar-Russell, Ph.D., the medical staff of the cardiac intensive care and progressive care units at Johns Hopkins Bayview Hospital, and the laboratory of Gayle Page, D.N.Sc., R.N.

I would also like to recognize USUHS administrative staff who helped support this research, either directly or indirectly, including MPS staff members Tricia Crum and Angela Carpenter and Krantz laboratory staff members Stephanie Garey and Briana Todd.

Finally, I am thankful to two MPS students in particular, Anna Ghambaryan and Christie Oates, who have always kept my best interests in mind, taken the time to truly listen, and encouraged me to move forward through this process.

This research was funded in part through a National Institutes of Health T32 Behavioral Cardiology Pre-doctoral Training Fellowship, TO funds from the USUHS Graduation Education Office, a dissertation award from the American Psychological Association, and an NIH P30 Award funding the JHU Center for Mind-Body Research.

Dedication

To my husband, Juan Carlos Arango Lasprilla,

for making my goals our goals, and

for sacrificing countless days, night, and even months

in pursuit of this accomplishment.

He is a constant reminder to me, through his own example,

that nothing that stands in the way of one's dreams is insurmountable

with drive, persistence, passion, and courage.

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Introduction

The prevalence in heart failure (HF) is increasing due to improved success rates of modern cardiac interventions and therapy and a larger aging the population (Vasan & Wilson, 2006). Despite improvements in therapy, HF mortality is high (Ho, Pinsky, Kannel, & Levy, 1993; Goldberg, Ciampa, Lessard, Meyer, & Spencer, 2007). HF is the leading source of morbidity and mortality in the elderly (Watson, Gibbs, & Lip, 2001). HF occurs when the heart cannot pump enough blood and oxygen to meet the needs of other body organs. HF is a progressive disorder that may occur after an abrupt "index event," as a result of a chronic, sub-clinical injury or insult to the heart, or due to cardiomyopathy. An index event such as myocardial infarction and a chronic insult with more gradual onset (e.g., high blood pressure leading to overload) both lead to HF via a decline in cardiac function and resulting decreased pumping capacity of the heart (Mann, 2004).

Medical, socio-demographic, and lifestyle risk factors for HF are well-established. Coronary artery disease (CAD) and hypertension are the chief contributors to HF in the general population (Eriksson et al., 1989; American Heart Association, 2006). Ischemic heart disease is the most common cause of HF (Lloyd-Jones et al., 2002), with inflammation identified as a risk factor and prognostic factor for heart disease. Inflammatory mechanisms also appear to play a pathogenic role in HF (Aurkust, Yndestad, Damas, & Gullestad, 2004; Pugh, Jones, Jones, & Channer, 2002). Psychosocial factors, such as depression, anxiety, anger/hostility, chronic stress, and lack of social support are increasingly recognized as important predictors of CAD etiology and prognosis (Rozanski, Blumental, & Kaplan, 1999; Rozanski, Blumenthal, Davidson, Saab, &

Kubzansky, 2005; Strike & Steptoe, 2004), however the influence of these factors in the development and maintenance of HF is more controversial and less understood.

In patients with HF, social support predicts cardiovascular mortality (Friedmann et al., 2006; Rohrbaugh, Shoham, & Coyne, 2006, Murberg, 2004), re-hospitalization (Schwartz & Elman, 2003; Chin & Goldman, 1997), and occurrence of future cardiac events (Krumholz et al., 1998). Preliminary analyses of Cardiovascular Health Study outcome data through 2000 suggest that one type of social support in particular may play an important role in incident HF (Rogers & Krantz, 2007), however, additional study is needed. Furthermore, the identification of potential bio-behavioral mechanisms, such as inflammatory marker levels, through which social support might influence HF warrant examination.

The background of the present proposal is divided into six sections. The first section will define HF and describe its epidemiology, etiology, and known risk factors. The second section will focus on social support. The various types of social support and their measurement will be explained. The two main theories posited to elucidate how social support may influence health will also be reviewed. In the third section, recent literature on the relationship between social support and cardiovascular disease development and processes will be examined and current knowledge on the link between social support and acute coronary syndromes and HF in particular will be discussed. Potential physiological mechanisms through which social support may influence heart failure have not been explored. Thus section four will focus on the role on inflammation in the development and progression of acute coronary syndromes and heart failure. Section five will cover findings linking social support to inflammatory markers in healthy individuals and people with disease. The sixth and final section will provide a synthesis of the

previous sections in the form of a theoretical model that guides the present research methodology.

Heart Failure

Definition

Heart failure occurs when the heart cannot supply enough blood and oxygen to meet the needs of other body organs. The American College of Cardiology (ACC) / American Heart Association (AHA) Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult defined HF as a "complex clinical syndrome than can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood" (Hunt et al., 2001). As a clinical syndrome, HF is characterized by symptoms and signs of increased water in tissues and organs (which cannot be pumped to other parts of the body because of the failing heart) and decreased perfusion of blood to tissues and organs, again as a result of inadequate heart pumping function (Zile & Baicu, 2004). Heart failure is a clinical syndrome and no single test can establish its presence or absence. Current diagnostic criteria from the ACC and AHA (Hunt et al., 2001) require the presence of symptoms such as dyspnea (shortness of breath), decreased exercise tolerance, and/or fluid retention **and** objective data obtained via echocardiogram (to identify anterior Q waves or left bundle branch block), chest radiograph (to detect an enlarged heart, or cardiomegaly), and possibly a radionucleotide angiography or contrast cineangiography, if the previous tests are inadequate or inconclusive.

HF is often, but not always, caused by an inability of the ventricles to properly contract, termed systolic dysfunction. Approximately one-third of patients with symptoms of HF have normal ventricular/systolic function. Symptoms of HF in this group are caused by abnormal

filling of the left ventricle, referred to as diastolic dysfunction (Kusumoto, 1999). Of the remaining two-thirds of individuals with HF, one third has systolic dysfunction and one third has combined systolic/diastolic dysfunction (Vasan, Benjamin, & Levy, 1995).

Epidemiology

Approximately 5 million Americans experience HF and nearly 23 million people are affected worldwide (American Heart Association, 2006). At least 550,000 new cases are diagnosed each year in the US, afflicting 1.5% to 2% of the total population and as much as 6% to 10% of the elderly population (American Heart Association, 2006). The Framingham study indicates that the lifetime risk of HF is 21% in men and 20% in women (Lloyd-Jones et al., 2002). The prognosis of HF is poor. Ten percent of adults with HF die within one year, while half die within five years (Cowie et al., 1997). A recent study of long-term survival after HF in the Worchester, MA metropolitan area (Goldberg et al., 2007) found that all-cause death rates were 37.3% at 1 year after discharge, 52.9% at 2 years and 78.5% at 5 years. For patients with incident HF, the cumulative death rates were 27.8%, 40.1%, and 62.5% respectively.

HF is now the leading diagnosis for hospitalization of people age 65 and older (DeFrances & Podgornik, 2006) and the leading source of morbidity and mortality in the elderly (Watson et al., 2001). The Centers for Disease Control and Prevention's (CDC) 2004 National Hospital Discharge Survey indicates that hospitalizations for HF have risen from 402,000 in 1979 to 1,101,000 in 2004 (DeFrances & Podgornik, 2006). HF is a major burden to patients, healthcare providers, and society. Up to 16% of people with HF are readmitted for HF within 6 months of first admission (Cowie et al., 1997). In the U.S. alone, expenditures in hospitals and

nursing homes, and for medical follow-up costs resulting from HF are estimated to exceed $29.6 billion per year (American Heart Association, 2006).

Etiology

As described previously, most HF is due to systolic dysfunction, or an inability of the ventricles to properly contract. In one third of patients, HF symptoms are caused by diastolic dysfunction, or abnormal filling of the left ventricle (Kusumoto, 1999). The pathophysiology of each type of HF may differ. Some selected causes of systolic and diastolic dysfunction in HF are listed in Table 1.

Table 1: Causes of dysfunction in HF (adapted from Kusumoto, 1999)

CAUSES OF SYSTOLIC DYSFUNCTION	CAUSES OF DIASTOLIC DISFUNCTION
Coronary artery disease	Coronary artery disease
Myocardial ischemia	Myocardial ischemia
Myocardial infarction	Hypertension
Metabolic conditions (e.g., diabetes mellitus)	Aortic stenosis
Chronic hypertension	Infiltrative cardiomyopathies
Abnormal heart valves	Genetic conditions
Infection	
Toxicity (e.g., alcohol, lead)	
Neuromuscular disorders	
Idiopathic	

HF is a progressive disorder initiated after an “index event,” chronic injury, or as a result of cardiomyopathy. A cardiomyopathy is a type of heart disease in which the heart muscle is abnormally thickened and/or stiffened or the chambers are slightly dilated. As a result of a cardiomyopathy, the heart muscle's ability to pump blood is usually impaired. HF may also be initiated by an index event, or an insult to the heart with abrupt onset, such as a myocardial infarction (MI). HF may also result from chronic insult of a gradual nature, such as high blood

pressure leading to an overworked heart or valvular disease. The index event or chronic insult causes the heart to stop contracting normally, either by causing heart cells to die or to change phenotype in a maladaptive manner, thus resulting in a decline in the pumping capacity of the heart (Mann, 2004).

Medical Risk Factors for HF

The time course of heart failure is quite variable, thus the ability to predict HF progression is difficult. However, hypertension and coronary disease are the chief causes of heart failure in the general population (Erikkson et al., 1989; CDC, 2005). Seven out of 10 people with HF had high blood pressure before being diagnosed (CDC, 2005). Systolic blood pressure is a better indicator than diastolic blood pressure at all ages and in both sexes, and pulse pressure has also been found to be a powerful predictor of HF risk (Kannel et al., 1999). Prior myocardial infarction is an important risk factor. Although the incidence of heart failure after myocardial infarction has fallen over the past few decades, approximately 22% of men and 46% of women develop HF within six years of having a heart attack (American Heart Association, 2006; Weir & McMurrary, 2006). Diabetes mellitus is an independent risk factor for HF (CDC, 2005) and is a greater hazard in women than men (Ho et al., 1993). Dyslipidemia (a high ratio of total cholesterol to high-density lipoprotein cholesterol) is an important predictor of coronary disease and heart failure (Kannel, et al., 1999).

Risk of HF increases linearly with the degree of thickening of the heart muscle's main pumping chamber, referred to as left ventricular hypertrophy (Aronow & Ahn, 1998; Gottdiener et al., 2000). Left ventricular hypertrophy may result from hypertension, obesity, diabetes, valve disease, or coronary disease. Valve disease, especially aortic stenosis, increases risk of HF

(Rahimtoola, Cheitlin, & Hutter, 1987). Electrophysiological changes in the heart, such as electrocardiogram ST-T segment abnormality and atrial fibrillation, predict HF. Markers of systemic inflammation [e.g., elevated C-reactive protein (CRP) levels] are also related to HF. For example, data from the Cardiovascular Health Study of community-dwelling older adults have shown that the three strongest independent predictors of heart failure were coronary artery disease, a systolic blood pressure greater than or equal to 140 mm Hg, and increased CRP levels (Gottdiener et al., 2000).

Physiologic Compensatory Responses to HF

Patients may remain asymptomatic or minimally symptomatic following an initial decline in pumping capacity because of the compensatory mechanisms that are activated in response to damage or decrease in function. The body's response to HF is complex and set into action to maintain the body's falling blood pressure that results from inadequate pumping of the heart. Neuro-hormonal activation is one set of responses that are activated when the heart can no longer pump at full capacity. Neuro-hormonal activation includes (a) stimulation of the sympathetic nervous system, (b) activation of the renin-angiotensin-aldosterone system, and (c) increased release of arginine vasopressin (AVP) (Kusumoto, 1999). It is now recognized that the major determinant of heart failure progression is the chronic overactivation of these compensatory systems of hormones (e.g., Torre-Amione, 2005). As HF progresses, additional responses include the release of hormones (e.g., natriuretic peptides A, B, and C) that are specific to the cardiac chambers, and the production and release of inflammatory cytokines. Each of these responses will be briefly explained below.

Sympathetic nervous system activation. The first acute neuro-hormonal response to HF is sympathetic nervous system (SNS) activation. It is considered a hallmark feature of HF (Mann, 2004). Norepinephrine levels become elevated, sometimes accompanied by increased dopamine and epinephrine levels as well. These hormones increase heart rate and cause arterial vasoconstriction and increased venous vascular tone, which help to maintain blood pressure. The parasymapathetic nervous system (PNS) is inhibited. Inhibition of the PNS in the sinus node causes increased heart rate, which also helps to maintain blood pressure.

Renin-angiotension-aldosterone system activation. Within hours of acute HF onset, juxta-glomerular cells in the kidney to begin producing increased renin. Renin promotes the degradation of angiotensinogen to Angiotensin I, which is then converted into Angiotensin II. Similar to norepinephrine, Angiotensin II causes arterial vasoconstriction. Unlike SNS activation, Angiotension II also causes sodium retention in the kidneys and other physiological effects designed to maintain blood pressure.

Arginine Vasopressin release. The posterior portion of the pituitary gland secretes increased arginine vasopressin (AVP) in response to continued heart failure. AVP is a vasoconstrictor that is more powerful than norepinephrine and Angiotensin II. AVP promotes renal re-absorption of water to maintain blood pressure.

Natriuretic peptide release. When HF is persistent and the above systems are activated for prolonged periods of time, natriuretic peptides help to restore the body's homeostasis. A, B, and C natriuretic peptides are stored in the atrium, ventricular, and vasculature respectively. These peptides are a downstream reaction to counteract the effects of the activated SNS, renin-angiotensin-aldosterone system, and AVP. A and B natriuretic peptides cause vasodilation and

excretion of sodium from the kidney (termed natriuresis). The physiological role of C natriuretic peptide is not yet clear, although it also appears to keep the renin-angiotension-aldosterone system in check (Colucci & Braunwald, 2005).

Inflammatory response. Activation of the inflammatory system also occurs in response to HF, and is hypothesized to contribute to the development and progression of HF (Mann, 2004), as will be detailed in section five of the background. Tumor necrosis factor-alpha (TNF-α), for example, is not found in normal heart tissue but is expressed in failing myocardium. Similarly, receptors for TNF- α in the myocardium are downregulated. Molecules like TNF- α are produced and released in order to recruit immune cells to a specific place to fight an antigen or repair an injury. They, and similar protein molecules called pro-inflammatory cytokines, stimulate cell division, proliferation, and differentiation to promote healing in the failing heart.

Non-medical Risk Factors for HF

Demographic and lifestyle risk factors. The prevalence of heart failure increases with age. Men have higher prevalence rates than women and African Americans have been shown to have higher prevalence rates than European Caucasians (CDC, 2005). Lower educational level is another demographic risk factor for HF (He et al., 2001). As previously described, approximately 30% to 50% of patients with heart failure are reported to have normal or nearly normal ventricular function (Vasan et al., 1995). Various population-based epidemiological studies show that this type of HF due to diastolic dysfunction affects disproportionately more women than men (e.g, Bursi et al., 2007; Devereux et al., 2000). For instance, in the Framingham Study, 65% of women's heart failure was due to diastolic dysfunction, while only 25% of men's heart failure was due to diastolic dysfunction (Vasan et al., 1995). Obesity contributes to heart failure directly

and indirectly, by promoting hypertension, left ventricular hypertrophy, dyslipidemia, diabetes, and insulin resistance (Lawlor, Lean, & Sattar, 2006). In the Cardiovascular Health Study, abdominal body fat distribution predicted HF (Gottdiener et al., 2000). The National Health and Nutrition Examination Survey III identified smoking and physical inactivity as additional lifestyle risk factors for HF (He et al., 2001).

Psychosocial risk factors. The role of stress as a risk factor for heart failure is controversial. Studies as far back as the 1950's have suggested that intense emotions might precipitate HF (Ghali, Kadakia, Cooper, & Ferlinz, 1988; Perlman, Ferguson, Bergum, Isenberg, & Hammarsten, 1971; Chambers & Reiser, 1953). In the Swedish study "Men Born in 1913", which began in 1963, the 17-year follow-up data showed that psychological stress predicted HF (Eriksson et al., 1989). However, later outcome data from that same cohort in 1996 did not support psychological stress as a predictor of HF (Wilhelmsen, Rosengren, Eriksson, & Lapps, 2001). High levels of psychological stress are significant predictors of hospital readmission (Levine et al., 1996) and high mortality (e.g., Murberg, Bru, Svebak, Tveteras, & Aarsland, 1999) in cardiac patients, but the relationship between stress and incident HF is not clear.

Depression was independently associated with a two-fold increased risk of developing HF among older individuals with isolated systolic hypertension (Abramson, Berger, Krumholz, & Vaccarino, 2001). Williams and colleagues (2002) found that depression was an independent predictor of HF development over a 14-year follow-up of 2501 elderly participants (HR = 1.96, 95% CI = 1.11–3.46) in women only. HF patients with depression have been found to have higher mortality rates and re-admission rates at three months and one year compared with patients who are not depressed (Jiang et al., 2001).

Social support has also been associated with hard outcomes (e.g., mortality and cardiovascular events) and soft outcomes (e.g. re-hospitalization), as will be described in the following sections. Moreover, preliminary analyses from Cardiovascular Health Study outcomes through 2000 suggest that one type of social support, poor social integration, is an independent predictor of incident HF in a population of community-dwelling elderly individuals (Rogers & Krantz, 2007).

Summary: HF is a growing clinical and public health problem. Initial problems in pumping capacity cause compensatory responses that include neuro-hormonal activation, natriutretic peptide release, and inflammatory responses. Medical, demographic, and lifestyle risk factors for HF are well established, but the impact of psychosocial factors such as social support in the development and progression of HF is less clear and needs further study.

Social Support

The term social support is a broad term that has been used in the scientific literature to describe both the structure of a person's social environment and the resources or functions such environments provide. The following section will describe structural and functional measures of social support and provide examples of how each is measured. At the end of the section, the main effect and buffering hypothesis theories will explain how social support may affect health and well-being.

Definition and Processes in the Social Support Construct

Structural social support refers to the size, density, complexity, symmetry, and stability of a person's family, friends, co-workers, and health professionals and community resources.

The terms *social integration/isolation* and *social network* and are often used to describe structural aspects of social support. The processes involved in this form of social support refer to participation in one or more social groups and contact with others through interactions without the purpose of exchanging help or support (Cohen, Underwood, & Gottlieb, 2000).

In contrast, the **functional component of social support** is defined as a person's perception of the availability of support and of the resources provided by one's network. This is the type of social support that most often tends to characterize the term *social support* (Shumaker & Czajkowski, 1994; Cohen et al., 2000). Within a social network, there is the provision or exchange of emotional, informational, or instrumental resources in response to the perception of need. Functional social support, then, refers to the social provisions that an individual perceives to be available, or that are actually provided to him/her, by non-professionals in the context of both formal support groups and informal helping relationships.

To review, structural social support or social integration measures such as social network size and social network participation or social integration measure the existence of and interconnections between social ties, whereas functional social support measures assess whether interpersonal relationships are viewed as serving a particular function (e.g., providing information or affection) (Cohen & Syme, 1985; Cohen & Willis, 1985). In general, social integration measures the quantity of social support and functional social support measures the perceived quality of support provided by one's network.

Structural Social Support

Structural measures include items such as marital status, number and frequency of contacts with family and close friends, church membership, and involvement in the community

and other groups (Cohen et al., 2000). Measures of social integration/isolation and social network are indicators of the structure of one's social environment and allow assessment of an individual's participation in one or more distinct social groups and their contact with others in general.

Social integration/isolation. Social integration, and its antithesis social isolation, is the extent to which an individual participates in a broad range of social relationships (Cohen et al., 2000). Social integration is a multi-dimensional construct that includes both a behavioral and cognitive component. Individuals who are socially integrated are actively engaged in a wide variety of activities and/or social relationships (behavioral component) AND have a feeling of communality with others and identify with their own social roles (cognitive component).

Measurement of social integration/isolation. Measures of social integration may be *role-based* or *participation-based*. Role-based measures assess the number of social roles or types of social relationships or social identities an individual holds. The Social Network Index (SNI) by Cohen and colleagues (1997), for example, assesses participation in 12 types of social relationships: spouse, parents, parents-in-law, children, other close relatives, close neighbors, friends, co-workers, classmates, fellow volunteers, members of non-religious groups, and members of religious groups. Active participation in the social relationship is operationalized as talking on the phone or in person with the above individuals at least once every two weeks. In contrast, *participation-based* measures of social integration assess the frequency with which individuals engage in various activities. Single items, such as number of visits with friends in a two week period, or types of activities, for instance active leisure activities like going to class or

playing sports, engaged in over a typical month are commonly used as markers of participation-based integration.

The Social Participation Scale (SPS; House, Robbins, & Metzner, 1982), taken from questions in the Tecumseh Community Health Study, is an example of a participation-based social integration measure. The SPS assess participation in four categories of social activity: (1) intimate social relationships (e.g., marital status, visits with friends and relatives); (2) formal organizations outside of work (e.g., going to church or community meetings); (3) active, social leisure (e.g., going to fairs and museums); and (4) passive, solitary leisure (e.g., watching TV or reading). Respondents are asked to estimate the frequency with which they have engaged in these activities over the past year. The first subscale is more of a role-based measure of social integration, while the remaining three scales are participation-based. In practice, it is often difficult to separate role-based and participation-based measures of social integration because social activities involve engagement with others and reflect a range of social ties, or role-based integration, as well.

Perceived integration. Another type of social integration is perceived integration. Perceived integration measures assess the extent to which individuals believe they are embedded in a stable social structure and identify with their fellow community members and social positions. Typical subscales that reflect perceived integration examine an individual's feelings of communality and belongingness. An example of a perceived integration measure is the social anchorage subscale of the Malmö Influence, Contact, and Anchorage Measure (MICAM; Hanson, Isacsson, Janzon, & Lindell, 1989) which consists of eight items and asks respondents to evaluate the degree to which they feel integrated into their communities. One item asks, for

instance, “Would you feel you are rooted and have a feeling of familiarity with your neighborhood?”

Complex indicators of social integration. Lastly, complex indicators of social integration combine information regarding marital status, social ties, community involvement, and frequency of contact with friends and relatives into a single summary index. Berkman and Syme’s (1979) Social Network Index (SNI) is a typical example of a complex indicator. It is a summary measure created from knowledge about marital status and a sociability index based on contact with friends and relatives, church membership, and group membership. The scoring of the SNI takes into account both the number and relative importance of social ties via weighting of the scores and then combines the information into a single total score. The weighting system is empirically-based and gives the index of intimate contacts four times the weight of group membership and twice the weigh of church membership.

Social networks. Social network is an indicator of structural social support. Specifically, the term network refers to the ties that connect a specific set of actors or nodes. Network analysis provides a quantitative way to describe the relationships that exist between members of an individual’s social network. Structure in a social network is the term used to describe stable patterns that exist among ties. The simplest and most widely used measure of network structure is network size (the number of people in the network). Network density refers to the extent to which network members know one another. High-density networks, in which network members are acquainted, may be beneficial in certain situations because they maintain one’s social identity and promote the flow of support resources from network members. Low-density networks may be advantageous in other situations and may be a characteristic of socially integrated individuals,

although very little is known about how network density relates to other processes of social support (Cohen et al., 2000).

An example of a social network measure is the Social Network List (SNL; Hirsch, 1979). Respondents must list up to 20 significant others with whom they have contact at least once every two weeks and indicate which people are relatives and friends (estimate of network size). Then respondents must list the individuals previously named in a matrix and identify the individuals they consider to have relationships with one another (estimate of network density).

Functional Social Support

Social relationships provide supportive functions or resources that (1) are perceived to be available if needed or (2) are actually received. Exchange or provision of resources within one's social network is a typical response to the perception of need, and needs often tend to be associated with acute or chronic stressful experiences.

Dimensions of functional social support. Several dimensions of functional social support have been delineated to describe the types of resources that may be available from the individuals who make up one's formal and informal social network. *Emotional support* is defined as sympathetic listening when an individual is having problems. Examples of emotional social support include demonstration of caring and acceptance towards the person in need. *Instrumental support* is practical help, for example assistance with transportation, help with household chores or child care, and/or provision of tangible aid (e.g., bringing tools or lending money). *Informational support* refers to knowledge that is useful for solving problems. Examples of informational social support include information about community resources and services or advice and guidance about alternative courses of action. *Companionship support* refers to people

with whom one can participate in social, leisure, cultural, or recreational activities. *Social comparison, feedback, or validation* refers to information about the appropriateness or normativeness of behavior (Cohen et al., 2000).

Measurement of perceived social support. Paper-and-pencil self-report questionnaires and interviews are the most common methods employed to assess perceived or received functional social support. The majority of questionnaires and interviews available in the literature assess perceived, not received, social support. Those few measures that assess received functional social support (e.g., the Inventory of Social Supportive Behaviors; Barrera, Sandler, & Ramsay, 1981) tend to be multi-dimensional, tapping into many of the various domains of social support, and ask respondents to indicate how many times in the past 30 days they have received specific supportive actions. Questionnaires that are used to measure perceived availability of social support are sometimes used to measure received support by changing the instructional set provided to the respondent.

Perceived social support scales and interviews vary in terms of their dimensionality and breadth. A one-dimensional questionnaire with little breadth might ask a subject if he/she has a confidant or someone with whom he feels very close and intimate (e.g., Williams et al., 1992). Another one-dimensional scale emphasizing perceived emotional support with slightly more breadth might assess the degree to which important thoughts and feelings can be shared with and accepted by a spouse, closest family member, and closest friend (e.g., Hobfoll & Leiberman, 1987). The Older American and Resources Inventory (OARS) is an example of a multi-dimensional scale assessing perceived emotional and instrumental support with greater breadth. The 6-item questionnaire includes items about having a confidant, feeling understood, having

someone who would help if one were ill or disabled, and having someone who would care if something happened (Fillenbaum & Smyer, 1981).

Some measures of perceived social support assess availability of various dimensions of support from a range of specific or non-specific sources. For example, the Perceived Support from Family and Friends (PSS; Procidano & Heller, 1983) asks respondents to about the availability of closeness, confiding, emotional support, problem-solving advice, and social companionship from family. These 20 items are then repeated to assess functional support from friends instead of family. The Interpersonal Support Evaluation List (ISEL, Cohen & Hoberman, 1983), on the other hand, assesses perceived support that is available in general, or social support that is not specific to any particular friend or family member. Respondents are asked to indicate the degree to which statements or hypothetical situations are true or false. All of the items are general and half of are worded in a positive manner (e.g., “If I wanted to have lunch with someone, I could easily find someone to join me.”) while the other half are negative (e.g., “I don't often get invited to do things with others.”). Lastly, some inventories (e.g., The Arizona Interview Schedule; Barrera, 1981) use a two-stage process in which the respondent first identifies people who he/she perceives to provide supportive functions and then rates the availability and adequacy of the support. In the UCLA Social Support Interview (Dunkel-Schetter, Folkman, & Lazarus, 1987) respondents are asked to identify a stressful situation and people who may provide support relevant to that situation. Respondents are probed about support from a parent, friend, and romantic partner or physician depending on the setting. Respondents must rate the extent to which each provides emotional, instrumental, and informational support.

Social Support and Health: Theory

Cohen and Willis (1985) developed a model to explain how social support might positively or negatively impact health. According to this theory, social relationships may directly impact health, termed the main effect hypothesis, or social relationships may moderate the negative impact of stress on health, which is referred to as the buffering hypothesis. In the main effect model, social relationships can influence health behaviors (e.g., compliance with diet, exercise or medication regimens), help change a person's exposure to certain risk factors, or affect access to better health care. In some cases, lack of social support and/or social isolation in itself can be considered a stressor, directly negatively impacting health through well-established pathways linking stress and disease (Baum, Gatchel, & Krantz, 1997; Watkins & Maier, 1999).

The "stress buffering hypothesis," on the other hand, suggests that social relationships affect health only by preventing responses to stressful events that would be damaging to one's health. The buffering hypothesis posits that social support influences (1) the primary appraisals of a stressful situation (e.g., evaluation of the situation as threatening), (2) the secondary appraisals (e.g., evaluation of resources to cope with the threat), and/or (3) the emotional, physiologic, and maladaptive behavioral responses to a stressor (Cohen & Willis, 1985). The above pathways are not mutually exclusive, and it is possible that social support may affect the appraisal of a stressful situation and a person's response to a situation deemed stressful.

Summary: Structural social support refers to the size, density, complexity, symmetry, and stability of a person's family, friends, co-workers, and health professionals and community resources. The terms social integration/isolation, or the extent to which an individual participates in a broad range of social relationships, and social network, or the number of people in one's

social network and the degree to which they know one another, are structural measures of social support. **Functional social support** refers to a person's perception of the availability of support and of the resources provided by one's network. Dimensions of functional social support include perceived and received emotional, instrumental, informational, and companionship social support. Social support is hypothesized to directly impact health by influencing health behaviors, affecting exposure to specific risk factors, and/or impact access to health care. On the other hand, social support may also moderate the negative impact of stress on health by preventing responses to stressful events that would be damaging to one's health.

Social Support and Cardiovascular Disease Outcomes and Processes

Psychosocial factors such as depression, anxiety, hostility, chronic stress, and lack of social support are increasingly recognized as important predictors of coronary heart disease (CHD) etiology and prognosis (Rozanski et al., 1999). Numerous systematic reviews and meta-analyses conclude that lack of social support is an important risk factor (e.g., Berkman, 1995; Hemingway & Marmot, 1999; Kuper, Marmot, & Hemingway, 2002; Smith, & Ruiz, 2002). This section will briefly review the epidemiological and clinical research linking lack of social support to development of CHD and hard endpoints such as mortality and myocardial infarction. The section will conclude with recent literature demonstrating the importance of social support in acute coronary syndromes and heart failure development and progression.

Social Support in Individuals without CHD

Both structural and functional forms of social support are associated with CHD incidence, initial cardiac events, and CHD-related mortality. Eng and colleagues (2002) studied

28,369 individuals and found that a multi-dimensional measure of structural social support predicted 10-year incident CHD (RR = 1.19, 95% CI 1.06–1.34). Rosengren and colleagues (2004) found that functional measures of social support such as perceived emotional social support and a composite measure of structural and perceived tangible social support predicted CHD incidence in a 15-year follow-up of "Men Born in 1933" Swedish cohort (RRs ranged from 1.7 to 2.2). In a 15-year follow-up of 2,603 individuals, network size and frequency of social contacts were not predictive of incident CHD, however the number of domains in which an individual had social contacts did predict CHD incidence in this study (RR = 1.50, 95% CI =1.1 –2.3) (Vogt, Mullooy, Ernst, Pope, & Hollis, 1992). Evidence from other studies also fail to support the relationship between specific, one-dimensional measures of structural social support and incident CHD. For instance, Reed and colleagues (1983) studied social networks in 4,653 Japanese men living in Hawaii and did not find a relationship with CHD over an 8-year follow-up. Similarly, Kawachi and colleagues (1996) studied 32,624 men in the US over four years and did not find social networks to be associated with CHD.

Data from prospective studies of individuals without established CHD demonstrate the importance of social support in predicting MI and CHD mortality. Orth-Gomer and colleagues (1993) found that both functional and structural social support were associated with suffering non-fatal MI or death from CHD in 736 Swedish men over a 6-year follow-up. Men lacking perceived emotional support had 3.8 times the risk and men who had contact with fewer numbers of people in a given week had 3.1 times the risk of suffering a non-fatal MI or death from CHD compared to men had higher levels of emotional and structural social support. House and colleagues (1982) also examined the ability of both structural and functional social support

measures to predict CHD death. In a sample of 2,754 individuals in the Tecumseh Community Health Study, those with higher numbers of social relationships and social activities were more likely to die from CHD over the 9- to 12- year follow-up. No significant association was found for perceived satisfaction with social relationships and CHD mortality in this sample. Some studies have identified gender differences in the relationship between social support and incident CHD. For instance, Kaplan and colleagues (1988) followed a group of 13,301 individuals in eastern Finland for five years and found that a multi-dimensional measure of structural social support predicted CHD mortality in men only (OR = 1.54, 95% CI = 1.21–1.95).

Multi-dimensional structural measures of social support appear to be stronger predictors of CHD onset and poor outcomes over long follow-ups than functional measures of social support. It is important to recognize that not all studies have included both structural and functional measures of social support. As reviewed above, there appears to be some evidence for the predictive value of functional social support as well (Lett et al., 2005). In fact, some argue (Seeman, 1996) that the notion that the quality of the social relationships is more important that the quantity has certain face validity.

Social Support in Individuals with CHD

Various domains of structural and functional social support have been shown to predict a 2- to 4- fold increase in mortality and cardiac morbidity in patients with established CHD. In terms of structural measures, network size (Brummet et al., 2001; Horsten, Mittleman, Wamala, Schenck-Gustafsson, & Orth-Gomer, 2000; Ruberman, Weinblatt, Goldberd, & Chaudhary, 1984), marital status (Williams et al., 1992; Chandra, 1983; Wiklund et al., 1988), and social participation (Irvine et al., 1999; Jenkinson, Madeley, Mitchell, & Turner, 1993; Murberg & Bru,

2001; Oxman, Freeman, & Manheimer, 1995; Orth-Gomer, Unden, & Edwards, 1988) have been found to predict mortality and/or fatal/non-fatal cardiovascular events in individuals with CHD. Numerous dimensions of perceived functional social support are also associated with mortality and events, including emotional support (Berkman, Leo-Summers, & Horwitz, 1992; Krumholz et al., 1998), marital quality (Orth-Gomer et al., 2000; Coyne et al., 2001), tangible social support (Woloshin et al., 1997), and general perceived functional social support (Gorkin et al., 1993; Welin, Lappas, & Wilhelmsen, 2000).

According to a review by Lett and colleagues (2005), studies that have directly compared the effect of structural vs. functional social support in predicting fatal/non-fatal cardiovascular events in individuals with established CHD have produced conflicting results. Some studies (e.g., Berkman et al., 1992; Gorkin et al., 1993; and Welin et al., 2000) suggest that perceived functional support measures are more predictive than structural measures, while others (e.g., Horsten et al., 2000; Williams et al., 1992; Murberg & Bru, 2001; Oxman et al., 1995) indicate that structural measures are more important the functional measures in predicting CHD events and mortality. Several reviewers (e.g., Rozanski et al., 1999; Sarason, & Sarason, 1994; Cummins, 1987), but not all (e.g., Lett et al., 2005; Seeman, 1996) support the latter view – that structural social support, but not functional support, is related to CHD progression.

Social Support and Acute Coronary Syndromes

The term “acute coronary syndrome” is used to describe a spectrum of conditions that involve chest pain or other symptoms caused by a lack of oxygen to the heart muscle, known as ischemia. Both acute myocardial infarction (MI) and unstable angina are forms of ACS. As reviewed previous, structural and functional social support are associated with the development

of acute coronary syndromes, with MI studied more than unstable angina. In patients with ACS, functional and structural social support is also an important predictor of outcomes.

Prognostic value of structural social support in patients with ACS. As early as 25 years ago, social support was identified as a risk factor for mortality in survivors of MI. Two thousand three hundred and twenty male MI survivors were interviewed as part of the β-Blocker Heart Attack Trial. Compared to those with low levels of stress and high social integration, men with high levels of stress and high levels of social isolation had a 4-fold increase in mortality (Ruberman et al., 1984). Since then, the risk associated with social isolation or having a poor social network has been found to be equivalent to many of the classic risk factors (e.g., elevated cholesterol levels, smoking, hypertension) as a predictor of 1-year mortality after MI (House, 2001). A recent systematic review by Mookadam and Arthur (2004) concluded that social isolation is associated with increased mortality and morbidity in individuals post-MI, with ORs ranging from 2.00 to 3.00. Excess morbidity and mortality is independent of other short-term (e.g., 6-month) and long-term (e.g., 6-year) predictors.

More recent studies also support the relationship between social support and progression of ACS, and structural measures of social support tend to have been studied more than functional measures. Dickens and colleagues (2004) assessed depression and social support in 1034 hospitalized patients within three to four days after MI. Social support was defined as having a close confident, someone the person was in contact with at least once a month with whom personal, sensitive information could be shared and from whom support could be provided. Although depression was prevalent in this sample (23.8%), depression was ***not*** associated with subsequent cardiac events over a 1-year follow-up, while those reporting a close confident had

0.57 times the risk (95% CI = 0.35–0.92) of having a subsequent cardiac events than those lacking a close confident, independent of demographic and coronary risk factors, severity of MI, and discharge medication. Schmaltz and colleagues (2007) studied the effect of living alone on mortality post-MI in 880 MI survivors hospitalized between 1998 and 1999. One hundred and sixty four survivors lived alone at admission and were more likely to be older and female than those living with others. Independent of risk factors and process-of-care variables, men living alone had a significantly increased risk of death over the 3-year follow-up (HR = 2.0, 95% CI = 1.1–3.7), but women did not (HR = 1.2, 95% CI = 0.7 – 2.2).

Prognostic value of functional social support in patients with ACS. Many studies examining psychosocial factors and CHD progression have been criticized for rarely including sufficient numbers of women. In one of the few studies to examine the relationship between functional social support and disease progression in patients with ACS, Wang, Mittleman, and Orth-Gomer (2005) recruited 102 women age 30 to 65 who were hospitalized with acute MI or unstable angina between 1991 and 1994 and tracked the progression of coronary atherosclerosis over three years. Women who lacked emotional support were found to have lumen narrowing of 0.15mm, women with social isolation had narrowing of 0.14 mm, and women with a lack of interpersonal social relationships had narrowing of 0.13 mm. Those women with high levels of emotional support showed less progression (0.05 mm), as did women who were socially integrated (0.07 mm) and women with more interpersonal social relationships (0.04 mm). The differences in coronary atherosclerosis progression between social support groups were significant, independent of age, smoking history, body mass index, menopausal status, and diagnosis of MI.

Social support and depression interactions on outcomes in patients with ACS. Other studies suggest that social support may indirectly influence the development and progression of ACS via an association with depression/anxiety, potentially leading to poorer outcomes. In a one-year follow-up study of depression and anxiety in 226 women after MI or coronary artery bypass graft surgery, the group of women who reported high levels of anxiety and depression that worsened over time also reported high levels of loneliness (Murphy et al., 2007). Similarly, Dickens and colleagues (2004) report that social isolation and lack of a close confidant are predictors of pre-infarct depression in 314 patients admitted to the hospital for incident MI. In an analysis of data from the "Men Born in 1914" Swedish study, André-Petersson and colleagues (2006) found that lack of social support was associated with increased risk of incident MI (HR = 2.40, 95% CI = 1.36–4.25) and premature death (HR = 1.99, 95% CI = 1.32–3.00) only in men who were classified as having a maladaptive behavioral response to a stressful situation.

Analyses of data from the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study of MI survivors with depression and/or low social support (ENRICHD Investigators, 2001) provide additional insight into the interaction between depression and social support on outcomes in this population. ENRICHD was a randomized controlled trial examining the influence of cognitive-behavioral treatment for depression and/or low social support on non-fatal re-infarction and all-cause mortality in a large, well-characterized cohort of patients enrolled within 28 days of MI. Barefoot and colleagues (2003) analyzed baseline and 1-year follow-up data from the ENRICHD pilot study and found that patients with high social support scores, and in particular those with high perceived support levels, had lower depression scores. High levels of perceived social support and low social conflict at baseline were associated with less Beck

cognitive depression over follow-up. Social networks and received social support did not influence depression in this study.

Using the entire ENRICHD dataset, Lett and colleagues (2007) found that only post-MI survivors without depression reporting higher levels of perceived functional social support were found to have improved outcomes (more time to death or non-fatal re-infraction) during the 4.5-year follow-up, independent of age, gender, race, socio-economic status, anti-depressant use, and a composite ENRICHD traditional risk factor score. High levels of perceived social support were not protective in the post-MI survivors with elevated depression levels. Also, in this study, neither perceived tangible social support nor social network measures were associated with adverse events (Lett et al., 2007).

Finally, data from ENRICHD and a control group of non-depressed MI survivors with adequate social support enrolled in an ENRICHD ancillary study (Carney et al., 2005) show a complex, non-linear interaction between depression and social support such that patients with high depression scores and high social support scores were at highest risk for re-infarction and all-cause mortality (Skala et al., under review).

Taken together, not only does social support appear to directly influence the development and progression of CHD and ACS, but these data provide evidence suggesting that lack of social support may serve as a stressor and/or support the buffering effect hypotheses, in which social support may buffer stress and its negative impact on disease processes. Few studies in the literature examining the relationship between social support and the development or progression of ACS occur while patients are still in the hospital. As reported in this section, Dickens and colleagues (2004) report that presence of a close confident reported three to four days after an

MI, but not depression levels during this time period, is an independent predictor of reduced risk of cardiac events over a 1-year follow-up. Further research is needed to understand the influence of social support on physiological markers of disease in patients with ACS within a few days of being hospitalized for MI or unstable angina.

Social Support and Heart Failure

Data from several small studies suggest that structural and functional forms of social support are related to hard and soft outcomes in individuals with previous or current heart failure. Murberg (2004) found that a measure of structural social support, perceived social isolation, predicted 6-year mortality (RR = 1.36, 95% CI = 1.04–1.78) in 119 patients with stable, symptomatic HF. Another measure of structural social support, being single, predicted hospital re-admission or death within 60 days of initial admission for HF in 257 patients (Chin & Goldman, 1997). Functional social support measures have also been studied in individuals with HF in relation to both hard and soft outcomes. Krumholz and colleagues (1998) found that a lack of emotional support was associated with a significantly higher risk of fatal and non-fatal cardiovascular events in the year after hospital admission for HF in women only. Absence of emotional support also contributed to re-hospitalization in the same sample of 292 patients with HF. Support of a caregiver reduced risk of hospital re-admission within three months in 128 patients with HF (Schwartz and Elman, 2003). Rodríguez Artalejo and colleagues (2006) studied 371 patients for an average of 6.5 months following initial hospitalization for HF and found that, compared to individuals with larger social networks, individuals with moderate and smaller social networks had 1.87 (95% CI = 1.06 – 3.29) and 1.98 (95% CI = 1.07 – 3.68) more risk of hospital readmission respectively, independent of socio-demographic, lifestyle, and medical

variables. Interestingly, this relationship was also independent of functional support measures such as perceived emotional support and perceived instrumental support. The magnitude of the association was similar or greater to that of other important predictors of re-admission, such as previous hospitalization.

However, not all studies support an association between social support and outcomes in individuals with HF. There was no relationship between structural or functional social support and mortality over the follow-up in the Rodríguez Artalejo and colleagues' study (2006). In a study by Bennett and colleagues (1997) of 62 patients with HF, perceived functional social support did **not** predict re-hospitalization within the 6-month follow-up. Some authors (e.g., Luttik, Jaarsma, Moser, Sanderman, & van Veldhusisen, 2005) hypothesize that social support was not predictive in this particular study because 73% of the patients were married, and most of the patients believed social support was available the majority of the time.

Research examining social support and heart failure provide evidence for a main effect of social support on HF development and progression, which is similarly seen in the review of the literature on social support and cardiovascular disease. There is some research to date to indicate that lack of functional social support and poor structural social support, i.e., social isolation, may function as stressors for individuals with HF. For instance, Coyne and colleagues (2001) found that individuals with HF living alone had greater psychological distress than those who were accompanied at home. Not living with family and poor perceived emotional-informational support were important predictors of psychological distress in another study of HF patients (Yu, Lee, Woo & Thompson, 2004). One implication that can be drawn from the findings of these two studies is that the presence of structural and functional social support may buffer the negative

effects of stress on HF, rather than directly influencing HF development and prognosis, although the interaction in HF patients had not been examined.

Preliminary analyses. Recently, we conducted preliminary analyses of data from the Cardiovascular Health Study (CHS) in order to assess the relationship between structural and functional social support and incident HF. CHS is one of the few recent prospective, large-scale, epidemiological studies to include measures of both structural and functional social support. The primary aim of CHS was to determine predictors of HF in a community-dwelling population of elderly individuals age 65 and older and the presence of heart failure was agreed upon by a CHS events committee consensus. Preliminary analyses of 4,901 CHS participants without HF at baseline showed that social isolation, but not lack of perceived functional social support, was a significant predictor of incident HF over follow-up through 2000 such that the risk of incident HF was 34% higher (HR = 1.34, 95% CI = 1.11–1.60) for individuals with social integration scores in the lower one third than individuals with social integration scores in the higher one third of the sample, independent of baseline age, coronary heart disease, hypertension, diabetes, smoking, and body mass index (Rogers & Krantz, 2007). Outcome data are now available from the National Heart, Lung, and Blood Institute through the year 2006, when CHS stopped collecting follow-up data on participants. This relationship needs to be confirmed using all outcome data.

Summary: There is considerable evidence to support the relationship between social support and the development and progression of CHD. The relationship between social support and the development and progression of acute coronary syndromes, and MI in particular, is also well established, but not in the population of individuals recently hospitalized for ACS. The

relationship between social support and progression of HF is less studied, but current findings are similar to those from the body of social support and cardiovascular disease literature. Little is known about the relationship between social support and incident HF, and preliminary analyses suggest the social isolation plays a role in the initial development of HF. Investigation into the bio-behavioral mechanisms through which social support might directly or indirectly influence HF development or exacerbation in both healthy individuals and those at-risk for HF is needed, and inflammatory processes in particular may provide an explanatory role in this relationship.

The Role of Inflammation in the Development and Progression of Coronary Disease, Acute Coronary Syndromes, and Heart Failure

Inflammation is the heart and vasculature's response to injury, pathogens, and/or a number of factors that include the aging process, hyperlipidemia, diabetes, smoking, hypertension, and genetic predisposition (Willerson, 2003). Inflammation may result directly from identification of an antigen in the cardiac tissue (e.g., in patients with myocarditis or cardiac allograft rejection) or occur secondary to cardiac injury (e.g., due to a myocardial infarction) and provides a healing function. Low molecular weight proteins, called cytokines, are the messengers of the immune response. Cytokines can be produced by many different cell types in numerous bodily tissues, including cardiac myocytes in response to cardiac injury and in the absence of immune system activation, and adipose cells. There are two basic types of cytokines: pro-inflammatory cytokines, which are involved in recruiting cells to an area to fight an antigen or repair an injury, and anti-inflammatory cytokines, which serve to shut off the immune response and maintain homeostasis. Pro-inflammatory cytokines include Interferon-γ, Tumor

Necrosis Factor – Alpha (TNF-α), Interleukin-1, and Interleukin-6 (IL-6). These pro-inflammatory cytokines magnify the inflammatory response by stimulating immune cell division, proliferation, and differentiation. For example, TNF-α induces the production of IL-6. IL-6, in turn, stimulates the production of acute-phase reactants such as C-reactive protein (CRP), serum amyloid, and fibrinogen. This is known as the cytokine cascade. C-reactive protein (CRP) is an acute-phase reactant that has received considerable study in the context of CHD development and progression. Each cytokine and acute-phase reactant has important biologic effects, as will be discussed later in the section. However, the amplification at each step in the cascade makes downstream biomarker indicators of a generalized low grade inflammatory state, such as CRP, particularly useful for diagnosis and prognosis in CHD.

Inflammation and Acute Coronary Syndromes

Acute coronary syndromes describe a spectrum of conditions caused by coronary artery disease (CAD) that include acute myocardial infarction (MI) and unstable angina. Recent research has shown that inflammation plays a key role in atherosclerosis, which is the primary cause of CAD and most cases MI. Atherosclerotic lesions or plaques, also known as atheromata, are asymmetrical focal thickenings of the intima, the innermost layer of the artery. This thickening consists of different types of cells, elements of connective tissue, lipids, and debris. Inflammatory and immune cells make up an important part of an ateroma (Stary et al., 1995). Many of the immune cells in the coronary plaque can be activated by microbes, auto-antigens, and various inflammatory molecules. The activated immune cells secrete inflammatory molecules, including TNF-α, that make the plaque unstable, weaken the fibrous protective cap, and make the plaque more likely to rupture (e.g., Frostegård et al., 1999). CRP has also been

found to influence lesion progression and stability of coronary atherosclerotic plaques (Virmani et al., 2003). Once the plaque ruptures, a thrombus is formed on the surface of the plaque. If blood flow through the coronary artery is obstructed, plaque rupture can elicit an acute coronary syndrome. Most cases of MI and unstable angina result from this thrombolytic process (Davies, 1996).

The inflammatory process occurring in the atherosclerotic artery may lead to increased blood levels of inflammatory cytokines and acute-phase reactants. Various studies have shown that systemic levels of inflammatory markers are elevated in patients with unstable angina or MI (see Wasserman & Shipley, 2006 for a review). Moreover, the higher the levels of the pro-inflammatory cytokine IL-6 and the acute-phase reactant CRP, the worse the prognosis for these ACS patients (Liuzzo et al., 1994; Biasucci et al., 1996; Lindahl, Toss, Siegbahn, Venge, & Wallentin, 2000). Recent work suggests that inflammatory immune activation in coronary arteries initiates acute coronary syndrome. Circulating levels of inflammatory markers, then, are thought to reflect the clinical course of the condition (Hansson, 2005). Furthermore, an elevated CRP level is an independent risk factor for CAD in healthy populations (Ridker, Hennekens, Buring, & Rifai, 2000; Danesh et al., 2004). In fact, several different inflammatory markers, with different biologic activities, contribute to the statistical risk of CAD. Therefore, CRP and other inflammatory markers are not likely causes of disease, but rather mirror the local inflammatory process occurring in the artery and possibly in other sites in the body (Hansson, 2005).

Inflammation and Heart Failure

As in acute coronary syndromes, patients with chronic heart failure are characterized by systemic inflammation, evidenced by elevated levels of pro-inflammatory cytokines such as

TNF-α and IL-6 that increase according to the degree of severity. Levine & colleagues (1990) were the first to detect elevated TNF-α levels in chronic HF patients over 25 years ago. Since then, numerous studies (e.g., Adamopoulos, Parissis, & Kremastinos, 2001; Testa et al., 1996) have demonstrated that HF patients have elevated circulating levels of inflammatory cytokines such as TNF-α, IL-6, and interleukin-1β. The increased plasma/serum levels of inflammatory cytokines are associated with deteriorating New York Heart Association functional class levels and decreasing cardiac performance (e.g., left ventricular ejection fraction) (Deswal, Bozkurt, & Mann, 2003). These inflammatory markers have also been shown to have prognostic value in patients with HF. Torre-Amione and colleagues (1996b) found that patients with lower TNF-α levels had better prognosis than those with higher levels. Levels of circulating TNF-α and IL-6 were independent predictors of mortality in patients with advanced HF from the Vesnarinone trial (Deswal et al., 2001). C-reactive protein (CRP) is a systemic marker of inflammation important that has been shown to correlate positively to adverse cardiovascular events (e.g., Ridker, Stampfer, & Rifai, 2001; Koenig et al., 1999), including HF (e.g., Sabatine et al., 2007). Moreover, CRP was the strongest independent predictor of HF in community-dwelling individuals of the Cardiovascular Health Study (Gottdiener et al., 2000) and a CRP serum level greater than or equal to 5 mg/dL was associated with a 2.8-fold increased in HF risk in the Framingham Study as well (Vasan et al., 2003).

The cytokine hypothesis. The known biological effects of pro-inflammatory cytokines can explain many aspects of the syndrome of HF. For instance, when TNF- α or IL-6 are expressed at sufficiently high concentrations, observed deleterious effects include left ventricular dysfunction, pulmonary edema, cardiomyopathy, endothelial dysfunction, left ventricular remodeling, and

reduced skeletal muscle blood flow (Kapadia et al., 1998; Deswal et al., 2003). As previously described, cytokines are the messengers of the immune system and tend to be expressed in waves, or cascades, in order to communicate the body's specific needs. In a cytokine cascade is part of the inflammatory response and refers to the sequence of expression of specific cytokines. For instance, in the cytokine cascade, TNF- α and Interleukin-1 expression directly simulates IL-6 secretion. IL-6 production activates the downstream acute phase reactant CRP.

Seta and colleagues (1996) have proposed a "cytokine hypothesis" for HF in which heart failure progresses in part as a result of the deleterious effects of cytokine cascades on the heart and peripheral circulation. TNF-α has biologic effects that mimic the HF phenotype when expressed at high concentrations. IL-6 is of interest in the study of HF because it is activated by TNF-α and expressed in the development of cardiac remodeling, a complex and dynamic process that occurs as a reaction to an injury or insult to the myocardium (e.g., a myocardial infarction) and contributes to the development of HF (Bril & Feuerstein, 2003). CRP is a downstream product of the cytokine cascade that amplifies the effects of other activators of inflammation. Although the biological plausibility of the association between CRP and HF is not well understood at present, CRP is a strong predictor of HF development after MI as will be reviewed in a later section. As in acute coronary syndromes, cytokines themselves do not appear to cause HF, but rather the over-expression of cytokine cascades appears to contribute to heart failure progression.

Site and source of cytokines in HF. Inflammation plays a major role in the development and maintenance of cardiovascular problems, including the transition from stable to unstable coronary heart disease syndromes and heart failure. Cytokines are implicated at various stages of

the path from atherosclerosis to plaque rupture, myocardial infarction remodeling, and heart failure. As described previously, a systemic inflammatory response accompanies acute coronary syndromes, and its presence is an index of further events (Toss, Lindahl, Siegbahn, & Wallentin 1997). High blood levels of pro-inflammatory cytokines such as IL-6 and IL-1 as well as TNF-α have been observed after myocardial infarction (Munkvad, Gram, & Jespersen, 1991; Guillen, Blanes, Gomez-Lechon, & Castell, 1995; Latini et al., 1994) and implicated in left ventricular remodeling in response to injury (Ono, Matsumori, Shioi, Furukawa, & Sasayama 1998; Swynghedauw, 1999), which can lead to HF.

There are numerous hypotheses that attempt to explain the site and source of these inflammatory markers of HF that have been detected at elevated levels in the systemic circulation of patients with HF. (1) Some form of tissue injury may activate the immune system and initiate the cytokine cascade. (2) Cardiac myocytes may directly synthesize and release pro-inflammatory cytokines, potentially in response to tissue injury, and elevated levels detected in the bloodstream may be a result of "spillover". (3) When the body's organs do not receive the blood and oxygen they need (under-perfusion of systemic tissues), pro-inflammatory cytokines may be elaborated. (4) Cytokines may be activated by toxins in an edematous, or swollen, bowel. (5) Pro-inflammatory cytokines in the heart and peripheral circulation may also become activated from the sustained neuro-hormonal activation that is the body's compensatory response to HF (Mann, 1999).

Prognostic Value of Inflammatory Markers in Patients with ACS

Reviews of the predictive value of inflammatory markers measured in patients with acute coronary syndromes suggest that CRP and IL-6 levels may be useful to stratify patients at high

risk of recurrent events or death and as indicators of which patients may benefit most from an early invasive strategy (Blake & Ridker, 2003). Data on the prognostic value of TNF-α is limited. One study by Ridker and colleagues (2000) indicates that TNF-α levels are persistently elevated in post-MI patients at increased risk for recurrent coronary events, suggesting that inflammatory instability is present even among stable post-MI patients an average of 8.9 months after MI.

However, not all research supports the association between inflammatory markers and recurrent coronary events after MI. For instance, Harb and colleagues (2002) found that, in stable post-MI patients, CRP measured two months after MI was **not** an independent marker for recurrent coronary events. Similarly, Sukhija and colleagues (2007) studied 249 patients admitted with acute chest pain who underwent coronary angiography and found that serum levels of CRP, IL-6, and TNF-α were not associated with either atherosclerotic burden or adverse cardiac events (MI, death, or coronary revascularization) over the 6-month follow-up.

Although the incidence of heart failure after myocardial infarction has fallen over the past few decades, epidemiological data from Olmsted County, MN suggest that at least 36% of patients experience heart failure after MI (Hellermann et al., 2003). Some reviews cite that HF is even more common, and present after MI in up to 45% of the cases (Weir & McMurrary, 2006). Despite emerging evidence of the role of inflammation in heart failure, there is a paucity of data regarding the prognostic value of inflammatory markers measured after MI in predicting later HF. At least three studies show that elevated levels of the systemic inflammatory marker CRP measured within 24 hours of MI symptom onset predict death and HF development over a 2-year follow-up (Kavsak et al., 2007; Suleiman et al., 2006). Bursi and colleagues (2007) provide

evidence of the dose-response, prognostic value of CRP after MI. Levels of CRP measured within 12 hours of hospital admission for MI were divided into tertiles. One year survival free from HF was 88% (95% CI = 81%-94%) in the lowest tertile, 72% (95% CI = 64%-81%) in the middle tertile, and 52% (95% CI = 43%-64%) in the highest tertile. Compared with MI patients in lowest tertile, patients in the higher tertiles had significantly increased risk of HF, independent of age, gender, and comorbidity.

Regarding the long-term prognostic value of inflammatory cytokines in predicting HF in acute coronary syndromes, data are sparse. Two studies from Spanish researchers have found relationships between cytokine levels and later HF in populations of MI survivors undergoing percutaneous coronary intervention (PCI) and angioplasty (Domínguez Rodríguez, Abreu, Garcia, & Ferrer, 2006; Domínguez Rodríguez, Abreu, Garcia, & Ferrer, 2005). Plasma levels of soluble TNF *receptor* type I following acute MI predict survival, and preliminary evidence suggests levels of this receptor predict later HF (Ueland et al., 2005).

Summary: Inflammation is now known to be a major driving force underlying the initiation of coronary plaques, their unstable progression, and eventual disruption. Inflammation also contributes significantly to thrombotic complications that occur in ACS. Levels of inflammatory markers are elevated in HF. Several pro-inflammatory cytokines, such as TNF-α and IL-6, mimic symptoms of HF when expressed at high concentrations, further emphasizing their potential importance in the maintenance, and possibly the development, of HF. CRP, a downstream systemic marker of inflammation, is a valid biomarker of coronary disease severity, predicts adverse cardiovascular events, and is a strong, independent predictor of HF in community-dwelling populations and ACS patients. In the next section, literature from the

psychoneuroimmunology field examining the influence of social support on these inflammatory markers will be examined.

Social Support and Inflammatory Markers

Recent reviews suggest that inflammatory processes may underlie the relationship between psychosocial factors, such as depression, anxiety, stress, anger, socio-economic status, etc., and cardiovascular disease development and progression (Rozanski et al., 2005; Strike & Steptoe, 2004; Kop, 2003). The relationship between inflammation and depression, specifically, has received the most attention in the study of cardiac patients. Results have been mixed. Some studies suggest a positive relationship between depression and pro-inflammatory cytokines TNF-α, IL-6, and/or CRP after MI (e.g., Appels, Bar, Bar, Bruggeman, & de Bates, 2000; Janszky, Lekander, Blom, Georgiades, & Ahnve, 2005; Miller, Freedland, Duntley, & Carney, 2005). However, other studies (e.g., Lesperance, Frasure-Smith, Theroux, & Irwin, 2004; Annique et al., 2005; Shimbo, Rieckmann, Paulino, & Davidson, 2006) did not find significant associations in ACS patients.

Social support has also been found to influence systemic levels of inflammatory markers in both healthy and diseased populations, although this relationship has not been studied in cardiac patients. Evidence of the association between inflammatory markers TNF-α, IL-6, and CRP and structural and functional social support will be reviewed below because inflammatory process may serve as one potential mechanism through which social support might influence the development and progression of HF.

Social Support and TNF-α

Only one study to date has examined the relationship between social support and levels of the pro-inflammatory cytokine TNF-α. Kiecolt-Glaser and colleagues (2005) measured the morning circulating inflammatory marker levels of 42 healthy, married couples. The couples were subjected to a conflict interaction one day and a social support interaction the next day. Larger increases in plasma TNF-α (and IL-6) after the conflict interaction were found in the couples with high hostility compared to the couples with low hostility. The results can be interpreted in many ways. Hostility could be a surrogate for perceived functional social support, with high hostile couples having little emotional social support and the low hostile couples having higher levels of emotional support. Interpreted in this way, the results suggest a potential buffering effect, but not main effect, of social support on inflammatory marker levels.

Social Support and IL-6

Considerably more research has been conducted on social support and the pro-inflammatory cytokine IL-6. In a community-based sample of 557 older adults, religious attendance (a surrogate measure of the structural social support measure social integration) was related to lower mortality rates and IL-6 levels (Lutgendorf, Rusell, Ullrich, Harris, & Wallace, 2004). In fact, IL-6 levels were found to mediate the prospective relationship between religious attendance and mortality in this sample. Costanzo and colleagues (2005) studied 61 ovarian cancer patients and found that social attachment (a measure of social integration) was associated with lower levels of IL-6 in peripheral blood. Lastly, as described in the previous paragraph, there were larger increases in plasma IL-6 (and TNF-α) levels the morning after a conflict than

after a social support interaction in high-hostile couples compared with low-hostile couples (Kiecolt-Glaser et al., 2005).

Social Support and CRP

C-Reactive Protein (CRP) is a downstream, systemic inflammatory marker that has been well-studied in relation to social support, especially in population-based epidemiological studies. In fact, epidemiological evidence supporting a relationship between social support measures and circulating levels of any inflammatory markers is strongest for CRP. Data from the National Health and Nutrition Examination Survey III from 1988-1994 show that, of the 556 individuals with diabetes in the Survey, those who reported **not** attending religious services in the past year (a surrogate marker of social isolation) were found to have elevated CRP levels compared to those diabetics who **had** attended religious services over the past year (a surrogate marker of social integration) (OR = 2.17, 95% CI = 1.15-4.09) (King, Mainous, & Pearson, 2002). A more recent examination of data from the MacArthur Successful Aging Study found gender differences in the relationship between social integration and CRP (Loucks, Berkman, Gruenewald, & Seeman, 2006). The MacArthur Aging Study is a longitudinal study of relatively high-functioning elderly aged 70 to 79. The social integration measure combined role-based and participation-based measures. The social integration score was calculated for each participant based on presence/absence of spouse, close relatives, and close friends, and yes/no answers to participation in religious services, participation in religious activities other than religious services, and participation in clubs or voluntary associations. Data from 380 men and 425 women showed social integration was negatively associated with CRP in men ages 70-79. Specifically, the least integrated quartile of male participants was 2.23 times (CI = 1.05-4.76)

more likely than the most integrated quartile to have a CRP level greater than 3.19 mg/L after adjusting for age, race/ethnicity, smoking, alcohol consumption, physical activity, body mass index, cardiovascular disease, other major or chronic conditions, physical functioning, socio-economic status, and depression. (However, social integration was not associated with resting levels of IL-6 in men or women in this sample.) The association of perceived functional social support and inflammatory markers has not yet been examined.

Summary: Inflammatory processes contribute to the development and progression of CAD, ACS, and HF. There is also research to link social support, and social integration in particular, to systemic levels of CRP and IL-6. Less research has been done linking social support to TNF-α, and no epidemiological investigations of this relationship exist to date in the literature.

Conceptual Model

Figure 1 describes the conceptual model guiding this research. The model posits that social support influences HF via an association with physiological, immune, and behavioral risk modulators. HF may develop directly as a result of risk factor/marker elevation and/or after the

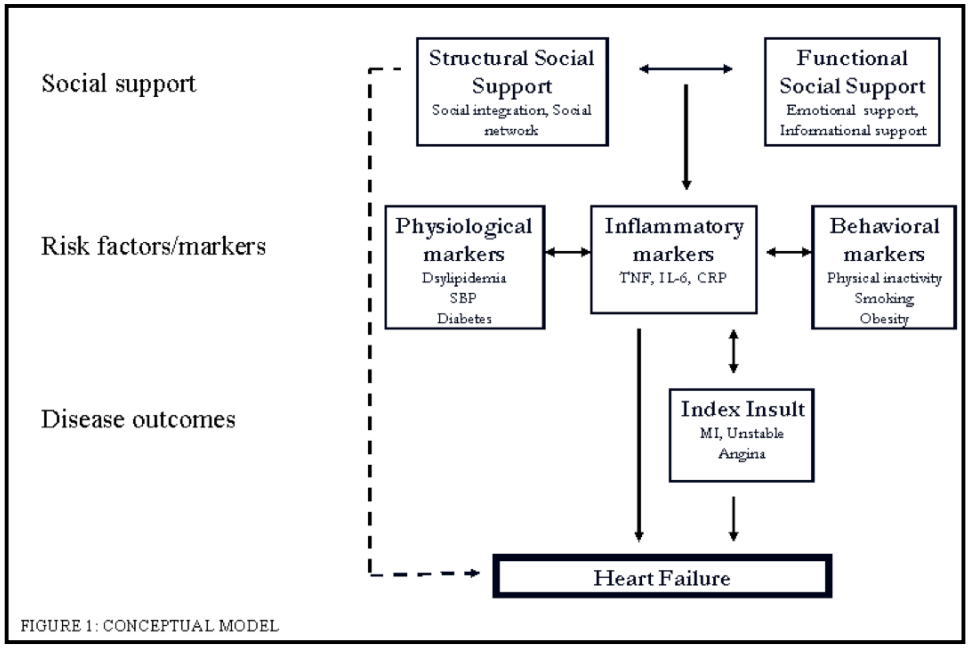

FIGURE 1: CONCEPTUAL MODEL

development of an index event (e.g., an acute coronary syndrome, including myocardial infarction or unstable angina).

The proposed research study methods were designed to test portions of this model via two separate studies examining structural and functional measures of social support and inflammatory markers in healthy, community-dwelling, older adults and individuals at risk for heart failure. To link social support to chronic inflammatory marker levels and later heart failure in a community-dwelling population, Study I involved the secondary analysis of longitudinal data collected in the Cardiovascular Health Study (CHS), a population-based epidemiological study of 5,888 community-dwelling older adults designed to determine predictors of HF with baseline data on structural and functional social support, as well as inflammatory markers IL-6 and CRP. We conducted pilot analyses using outcome data from CHS through 2000 and found that poor social integration was an independent predictor of incident HF, controlling for baseline age, coronary heart disease, hypertension, diabetes, smoking, and body mass index (Rogers & Krantz, 2007). However, Study I was limited in the inflammatory markers measured and did not allow an examination of the influence of social support on inflammatory markers at the time of an index event that puts an individual at risk for heart failure. Nor did Study I permit an in-depth study of various sub-domains of social support, including emotional and tangible perceived social support, total network size and number of embedded social networks. Therefore, Study II aimed to determine the relationship between inflammatory markers and structural and functional measures of social support in individuals within two days of suffering an acute coronary syndrome (myocardial infarction or unstable angina).

Study I: Secondary Analysis of Cardiovascular Health Study Archival Data

Specific Aims and Hypotheses

The specific aims of Study I were:

1. To further explore preliminary findings indicating that social integration is an independent predictor of incident HF in a community-dwelling population of elderly individuals using outcome data from the end of the CHS (through 2006).
2. (a) To examine the association between social support measures and inflammatory markers IL-6 and CRP. (b) Secondarily, to examine the association between social support measures and traditional risk factors for HF.
3. To determine if inflammatory markers IL-6 and CRP mediate the relationship between social support measures and HF.

The hypotheses of Study I were:

1. Poor social integration, but not functional social support, will be a predictor of HF, independent of age, race/ethnicity, coronary heart disease status, hypertensive status, diabetes status, smoking status, and body mass index. **Rationale:** Multi-dimensional measures of structural social support are related to incident coronary disease (e.g., Eng et al., 2002; and general consensus in the literature (e.g., Rozanski et al., 1999) is that structural measures are better than functional measures at predicting cardiovascular disease events and mortality.
2. (a) Social integration, but not functional social support, will be inversely associated with both IL-6 and CRP. **Rationale:** Prospective, community-based studies have found that structural social support is related to IL-6 (Lutgendorf et al., 2004) and CRP (Loucks,

Berkman, Gruenewald, & Seeman, 2006; King et al., 2002). (b) Poor social integration will also be associated with BMI and disease risk factors for HF such as coronary disease, hypertension, and diabetes. **Rationale:** Cytokines are implicated in the development and progression of coronary disease (Hansson, 2005), are produced in response to diabetes and hypertension (Willerson, 2003) and can be produced by adipose tissue, as well as failing myocardium.

3. IL-6 and CRP will mediate the relationship between social integration and HF. **Rationale:** Lutgendorf and colleagues (2004) found that IL-6 levels mediated the relationship between religious attendance, a surrogate for social integration, and mortality, suggesting that IL-6 and the downstream acute-phase reactant CRP may account for the effects of social integration on incident HF, which is a syndrome characterized by immune activation and persistent inflammation (Yndestad et al., 2006).

Study I: Methods

Sample

Data was extracted from the Cardiovascular Health Study (CHS), a prospective population-based study of 5,888 community-dwelling elderly people ages 65 to 100 (Fried, et al., 1991). Recruitment began in 1989 and all participants have been follow-up through 1999 (with events recorded until 2006) or death. The limited access dataset provided by the National Heart, Lung, and Blood Institute has been updated with events through 2006. Participants for CHS were recruited based on a random sample from Health Care Financing Administration files in 4 study sites (Sacramento County, CA, Washington County, MD, Forsyth County, NC, and Allegheny

County, PA). Participants were eligible to participate if they (1) were at least 65 years old, (2) were not institutionalized, (3) expected to remain in the area for 3 years, and (4) were able to provide and gave informed consent (Fried et al., 1991).

Participants in the Cardiovascular Health Study had a mean age of 72.4 years (sd = 5.5). Of the 5,888 participants, 2,495 were men and 3,393 were women; 687 were African Americans, who were recruited as a separate cohort in 1992 (Gottdiener et al., 2000).

Assessment of Social Support

Perceived social support was measured using a six-item version of the Interpersonal Support Evaluation List (Heitzmann & Kaplan, 1988 adapted from Cohen & Hoberman, 1983) and social integration was measured using the ten-item Lubben Social Network Scale (LSNS; Lubben, 1988).

The Interpersonal Support Evaluation List (ISEL) was adapted from a 40-question scale of the same name by Cohen and Hoberman (1983). This six-question ISEL asks respondents whether a given statement is definitely true, probably true, probably false, or definitely false. Examples of statements include: “When I am lonely, there are several people I can talk to.” “If I were sick, I could easily find someone to help me with my daily chores.” “When I need suggestions on how to deal with a personal problem, there is someone I can turn to.” For each response, 4 points were awarded for a definitely true answer, 3 for probably true, 2 for probably false and 1 point for definitely false responses. After reverse coding one item, a total perceived social support score was calculated by summing the responses to each of the 6 items so that higher scores reflected higher levels of perceived social support. The ISEL-40 and various shortened versions have been used widely in health-related research. For the 40-version ISEL,

alpha and test-retest reliability are approximately 0.90. For the sub-scales, internal consistency and test-retest reliabilities range from 0.70 to 0.80 and they are moderately inter-correlated (Cohen & Hoberman, 1983).

The LSNS assesses family relationships (3 items regarding size and frequency of contact), relationships with friends (3 items, similar to family questions), and interdependent relationships (4 items) such as the presence of a confidante. A validation study found that the LSNS possessed acceptable internal consistency levels ($\alpha = 0.76$) (Anastasi & Urbina, 1987). The summed responses to the individual questions (possible scores on the LSNS range from 0–50) have been used to represent a total social network score, which was found to be a robust predictor of lower multivariate-adjusted mortality (RR = 0.92, 95% CI = 0.86–0.98), controlling for age, comorbid disease, body mass, smoking, depression, and education in a sample of 7524 community-dwelling Caucasian women (Rutledge, Matthews, Lui, Stone, & Cauley, 2003). Ceria and colleagues (2001) found a significant dose-response relationship between LSNS score and six-year total all-cause mortality in the Honolulu Heart Study, independent of age and smoking status.

The total score on each social support measure was used in the primary data analyses as an indicator of perceived social support or social integration. Both questionnaires were administered at baseline and annually during Years 3 to 6 and again in Year 11 (see Table 2).

Assessment of Heart Failure

Heart failure was the primary outcome in the present study and was recorded in the Cardiovascular Health Study database for a participant if (1) he/she was diagnosed with HF by a physician and (2) a conformational review of the participant's medical records showed he/she

had received treatment for HF, which included a prescription for a diuretic agent and either digitalis or a vasodilator. In addition, symptoms, signs, and chest x-ray were reviewed by the CHS Events Committee, who classified all cardiovascular events (Gottdiener et al., 2000).

Table 2. Summary of measures and their times of administration within CHS

YEARS:	**BL**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Social Support	X	X	X	X	X					X
CRP	X			X						
IL-6	X									
Total cholesterol and HDL-C	X			X						
Fasting glucose	X			X						X
Fasting insulin	X			X						
Blood pressure	X	X	X	X	X	X		X	X	X
Anthropometric measures	X			X						
Medical and personal history	X	X	X	X	X	X	X	X	X	X

Assessment of Inflammatory Markers

The inflammatory markers C-Reactive Protein (CRP) and Interleukin – 6 (IL-6) were secondary outcomes and mediating variables in the present study. Blood was collected from participants in the morning after a 12-hour overnight fast at Baseline, Year 5 and Years 9, 10, and 11 (Fried, et al., 1991). Samples collected at Baseline and Year 5 were assayed by CHS to determine levels of CRP (see Table 2). The Baseline blood sample was also assayed by CHS to determine IL-6 levels (see Table 2).

Assessment of Physiological Measures

Total cholesterol levels, high density lipoprotein levels, and fasting glucose and insulin levels were obtained from the Baseline and Year 5 blood sample. Fasting glucose levels were also obtained on Year 11 blood. Fasting glucose levels were used by the CHS committee to determine diabetes status according to the American Diabetes Association (ADA) clinical practice recommendations the year when the blood was drawn. Fasting glucose was classified as impaired if levels were between 110 mg/dl and 125mg/dl and as diabetes if levels were greater than or equal to 126 mg/dl. Fasting glucose levels less than 110 mg/dl were considered normal per the ADA guidelines.

Blood pressure was measured almost annually (all years except Year 8). A decision of borderline hypertension was made by CHS if average seated systolic blood pressure was between 140 and 159 mmHg or average seated diastolic blood pressure was between 90 to 94 mmHg. A decision of hypertension was made if average seated systolic blood pressure was greater than or equal to 160 mmHg or average seated diastolic blood pressure was greater than or equal to 95 mmHg or if the participant had a history of hypertension and was currently taking hypertensive medication. If a participant had an average seated systolic blood pressure less than 140 mmHg and an average seated diastolic blood pressure less than 99 mmHg and was not taking anti-hypertensive medication, he/she was classified as normotensive. For the present study, following CHS recommendations, individuals with borderline hypertension and hypertension will be considered hypertensive.

Assessment of Demographic and Lifestyle Measures

Personal data, such as gender, race, marital status, education, income levels, etc. were obtained annually. Medical data were also obtained annually, including questions about past and current smoking status. For the present analyses, individuals who answered "yes" to the question "Did you ever smoke?" were considered smokers. Presence or absence of coronary disease was obtained via self-report. Self-reported disease status was confirmed via consultation of medical records by the CHS committee and a modified variable was created to show verified baseline disease status, reflecting changes over the course of the study based on medical verification. This modified baseline variable was used for analyses in the present study.

At baseline and year 5, weight, standing height, waist circumference, and hip circumference were measured, with weight and height used to calculate body mass index (BMI). (See Table 2.)

Study I: Data Analyses

As seen in Table 2, all variables were obtained at Baseline and all except IL-6 again at year 5. The specific aims were tested at baseline.

Primary Data Analyses

For Specific Aim 1, Cox regression analyses was used to determine if poor social integration predicts incident HF, independent of baseline age, race/ethnicity, coronary heart disease status, hypertensive status, diabetes status, smoking status, and BMI. For Specific Aim 2, correlational analyses were used to determine if social support measures were associated with inflammatory markers IL-6 and CRP. Separate Analyses of the Variance (ANOVAs) were then

conducted to examine the relationship between quartiles of social support and inflammatory markers. Traditional HF risk factors levels were associated with high and low social integration levels in chi squares or independent t-tests, depending on the continuous or categorical nature of the risk factor variable. For Specific Aim 3, to determine if inflammatory markers IL-6 and CRP mediated the relationship between social support measures and HF, Cox regression analyses were used following the procedure for testing a mediational model via methodology proposed by Baron and Kenny (1986).

Secondary Data Analyses

Gender differences in these relationships were examined because of research suggesting that social support and cardiovascular disease processes differ between males and females. Men are most often studied in large-scale studies of social support and cardiovascular disease. Research suggests that the relationship between social support and incident CHD exists in men only (Kaplan et al., 1988). In individuals with HF, lack of emotional support was associated with a higher risk of fatal and non-fatal cardiovascular events in women only (Krumholz et al., 1998). Preliminary analyses of CHS outcomes through 2000 provide evidence for a relationship between social integration and incident HF in both genders (Rogers & Krantz, 2007). In the MacArthur Aging Study, social integration was negatively associated with CRP in men only (Loucks, Berkman, Gruenewald, & Seeman, 2006). Thus CRP, and possibly IL-6 as one pre-cursor of CRP, was expected to mediate the relationship between social integration and incident HF in men only.

Study I: Power Analyses

Loucks, Sullivan, D'Agostino and colleagues (2006) studied the relationship between social networks (using the Berkman-Syme Social Network Index) and serum concentrations of the inflammatory markers IL-6 and CRP in 3,267 Framingham study participants. Controlling for age, smoking, blood pressure, total HDL-to-cholesterol ratio, BMI, medications, diabetes, cardiovascular disease, depression, and socio-economic status, IL-6 was inversely related to social network scores in both genders, while CRP was inversely related to social network in men only. Using the means and standard deviations of inflammatory markers from individuals in the highest and lowest social network quartiles, effect sizes were calculated for males and females. In both men and women, the relationship between IL-6 and social network was strong (r=0.72). A sample size of 15 of each gender have would allowed such a large effect size to be detected at 88% power and α=0.05. The relationship between CRP and social networks differed for men and women in the analyses of the Framingham participants. For men, the relationship between CRP and social network was r=0.38, and a sample size of 46 men would have been needed to detect such an effect at 80% power and α=0.05. For women, the relationship between CRP and social support network was considerably weaker (r=0.09), suggesting a sample size of 800 women would have been necessary to detect such a small effect at 81% power and α=0.05. There is no current literature examining the relationship between social support and TNF-α. However, the relationship between depression and TNF-α in HF patients (Parissis et al., 2004) suggests a large effect size (r=0.89). A sample size of 15 would have been sufficient to detect an effect size of that magnitude at 98% power and α=0.05. In CHS, there were 2,334 males and 3,187 females

free of HF at baseline, thus the analyses proposed to test the specific aims were sufficiently powered.

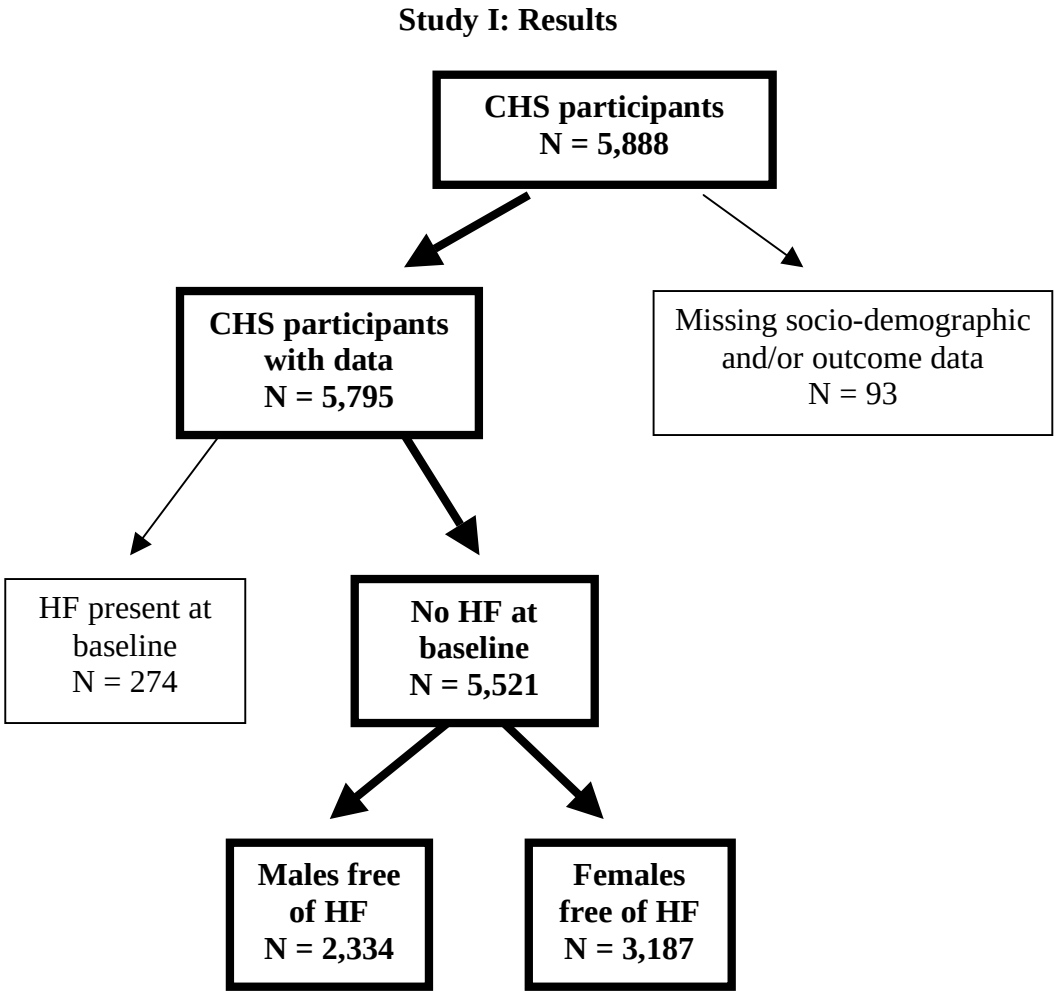

Figure 2: Breakdown of CHS sample

Description of the sample

Of the 5,888 participants enrolled in the Cardiovascular Health Study, ninety three CHS participants were missing socio-demographic and outcome data and were excluded from all analyses. See CHS sample breakdown in Figure 2. Two hundred and seventy four (4.7%). of the community dwelling elderly participants in the Cardiovascular Health Study had heart failure at baseline. These individuals were excluded from all analyses predicting incident heart failure. The final sample consisted of 5,521 participants free of HF at baseline broken down in to 2,334 males and 3,187 females. The baseline socio-demographic, medical, lifestyle, and social support characteristics of the male and female samples are presented in Table 3.

Table 3: Baseline characteristics of male and female sub-samples*

	MALES	**FEMALES**
Median age	69-70 years	67-68 years
Race:		
Caucasian	85.9%	82.8%
African American	13.5%	16.6%
Other	0.6%	0.6%
Marital status:		
Married	83.0%	54.4%
Widowed	10.1%	34.5%
Divorced, separated, other	3.8%	6.2%
Never married	3.0%	4.8%
Median educational level	High school graduate	High school graduate
Median income	$16,000-$24,999	$16,000-$24,999
Coronary disease	22.5%	13.7%
Hypertension	56.0%	60.2%
Diabetes	18.5%	13.8%
Smoking		
Never smoked	32.1%	56.8%
Former smoker	56.5%	30.4%
Current smoker	11.4%	12.8%
Mean body mass index	26.4 kg/m^2 (SD=3.5)	26.7 kg/m^2 (SD=4.4)
IL-6 levels	2.31 (SD=1.9)	2.07 (SD=1.9)
CRP levels	3.46 (SD=6.7)	3.56 (SD=5.7)

Social integration scores	31.43 (SD=7.0)	31.99 (SD=7.0)
Perceived social support scores	21.40 (SD=2.8)	21.67 (SD=2.7)
* Significant differences were found between males and females on all variables at $p < 0.01$		

Of the 5,521 individuals free of HF at baseline, 1,247 (22.6%) had incident HF over the follow-up. The risk of incident HF by year 1 was 2.3%, the risk of incident HF by year 5 was 15.1%, and the risk of incident HF by year 10 was 43.4%. The mean time to incident heart failure was 9.5 years. Of the 3,187 females free of HF at baseline, 636 had incident HF over follow-up. The risk of incident HF for females by year 1 was 1.9%, 13.1% by year 5, 40.4% by year 10. The mean time to incident heart failure for females was 9.7 years. Of the 2,334 males free of HF at baseline, 611 had incident HF during follow-up. The risk of incident HF for males by year 1 was 2.7%, 17.5% by year 5, and 47.0% by year 10. The mean time to incident heart failure for males was 9.2 years.

Specific Aim 1: Social integration as a predictor of incident HF

Social integration and incident HF. The first aim of Study I was to further explore preliminary findings indicating that poor social integration was an independent predictor of incident HF in a community-dwelling population of elderly individuals. Unlike previous analyses (e.g., Rogers & Krantz, 2007) conducted on a partial dataset, the present analyses were conducted with CHS outcome data through the end of the study follow-up in 2006. A quartile split of the total social integration score was used to compare time-to-incident-HF of individuals with higher and lower social integration scores. Kaplan Meier analysis indicated a marginally significant relationship between total social integration score and time-to-HF such that those in the highest quartile of social integration scores had the least time-to-HF compared to the other 3

quartile groups (log rank = 6.52, df = 3, $p < 0.10$). Perceived social support scores were not related to incident HF.

Social integration and HF: Gender differences. Because prior studies have revealed gender differences in the influence of social support on cardiovascular disease processes (e.g., Krumholz et al., 1998; Loucks, Berkman, Gruenewald, & Seeman, 2006), the univariate relationship between social integration and incident HF was examined within males and females. Using a quartile split of social integration scores, Kaplan Meier analyses indicated a significant relationship between total social integration score and time-to-HF in males, but not females, such that the those males in the highest quartile of social integration scores had the least time-to-HF compared to the other 3 quartile groups (males: log rank = 7.97, df = 3, $p < 0.05$; females: log rank = 1.03, df = 3, p = NS). See Figures 3 and 4. Perceived social support scores were not associated with incident HF in either males or females.

Figure 3: Social integration and time-to-HF in males

Figure 4: Social integration and time-to-HF in females

Cox regression analyses confirmed that social integration quartile scores significantly predicted incident HF in the male sub-sample only (Wald statistic = 7.91, df = 3, $p < 0.05$), while perceived social support did not. The relationship occurred in a dose-response fashion, such that the risk of HF was 43% higher for individuals with social integration scores in the lowest quartile than for individuals with social integration scores in the highest quartile the sample [HR = 1.43 (1.11-1.85), $p < 0.01$], 32% percent higher for the low-mid quartile compared to the high [HR = 1.32 (1.01-1.72), $p < 0.05$], and 22% percent for the high-mid quartile compared to the high [HR = 1.22 (0.94-1.58), p = NS].

Social support and HF controlling for traditional risk factors. Cox regression analyses were used to determine if social integration or perceived functional social support were independent predictors of incident HF. The established socio-demographic, medical, and lifestyle risk factors for HF entered into the model included baseline age, race, coronary heart disease status, hypertensive status, diabetes status, smoking status, and body mass index. The social support variable was entered last into the model.

Beyond traditional risk factors for HF, social integration was a significant independent predictor of incident HF (Wald statistic = 11.53, df = 3, $p < 0.01$) in a dose response fashion such that the risk of HF was 35% higher for individuals with social integration scores in the lowest quartile than for individuals with social integration scores in the highest quartile the sample [HR = 1.35 (1.13 – 1.61), $p < 0.001$], 24% percent higher for the low-mid quartile compared to the high [HR = 1.24 (1.03 – 1.49), $p < 0.05$], and 22% percent for the high-mid quartile compared to the high [HR = 1.22 (1.02 – 1.46), $p < 0.05$]. This relationship was present only in males [HR = 1.60 (1.24 – 2.08) for lowest vs. highest quartiles of social integration, $p < 0.001$], but not among females. Table 4 shows the relative strength of each predictor in predicting time-to-incident HF in males.

When current smoking status was entered into the Cox regression model for the sample (instead of smoking defined as ever having smoked), current smokers were 1.25 times more likely than non-smokers to develop HF over follow-up [adjusted HR = 1.25 (1.03 – 1.76), $p < 0.05$]. The effect of this change on the relationship between social integration and HF was minimal. Social integration was a significant independent predictor of incident HF (Wald statistic = 11.92, df = 3, $p < 0.01$) in a dose response fashion such that the risk of HF was 36%

higher for individuals with social integration scores in the lowest quartile than for individuals with social integration scores in the highest quartile the sample [HR = 1.36 (1.14 – 1.62), $p < 0.001$], 24% percent higher for the low-mid quartile compared to the high [HR = 1.24 (1.03 – 1.49), $p < 0.05$], and 22% percent for the high-mid quartile compared to the high [HR = 1.22 (1.03 – 1.46), $p < 0.05$].

Table 4: Cox regression model predicting time-to-incident heart failure in males

Variable	β	SE	Wald	df	*p*	HR (95% C.I.)
Age (65-70 yrs.)			42.28	3	<0.001	
Age 1 (71-76 yrs. vs. 65-70 yrs.)	0.19	0.11	2.85	1	<0.10	1.21 (0.97-1.50)
Age 2 (77-82 yrs. vs. 65-70 yrs.)	0.74	0.12	37.09	1	<0.001	2.09 (1.65-2.65)
Age 3 (≥ 83 yrs. Vs. 65-70 yrs.)	0.61	0.19	10.43	1	<0.001	1.85 (1.27-2.68)
Race			1.83	2	NS	
Race 1 (African American vs. Caucasian)	0.24	0.71	0.11	1	NS	1.27 (0.32-5.14)
Race 2 (Other vs. Caucasian)	0.44	0.73	0.36	1	NS	1.55 (0.37-6.41)
Coronary disease	0.56	0.10	33.53	1	<0.001	1.75 (1.45-2.11)
Hypertension	0.25	0.10	6.99	1	<0.01	1.28 (1.07-1.55)
Diabetes	0.32	0.11	8.77	1	<0.01	1.38 (1.11-1.70)
Smoker	-0.02	0.10	0.06	1	NS	0.98 (0.81-1.18)
Body mass index	0.05	0.01	16.56	1	<0.01	1.06 (1.03-1.08)
Social integration			**14.55**	**3**	**<0.01**	
Social integration (mid-high quartile vs. high)	0.35	0.14	6.51	1	<0.05	**1.41 (1.08-1.84)**
Social integration (mid-low quartile vs. high)	0.44	0.14	9.80	1	<0.01	**1.55 (1.18-2.03)**
Social integration (low quartile vs. high)	0.47	0.13	12.79	1	<0.001	**1.60 (1.24-2.08)**

In the male sub-sample, current smokers were 1.53 times more likely than non-smokers to develop HF over follow-up [adjusted HR = 1.53 (1.14 – 2.05), $p < 0.01$]. The effect of this change on the relationship between social integration and HF was also minimal. Social

integration was a significant independent predictor of incident HF (Wald statistic = 15.02, df = 3, $p < 0.01$) in a dose response fashion such that the risk of HF was 61% higher for males with social integration scores in the lowest quartile than for males with social integration scores in the highest quartile the sample [HR = 1.61 (1.25 – 2.09), $p < 0.001$], 56% percent higher for the low-mid quartile compared to the high [HR = 1.56 (1.19 – 2.05), $p < 0.01$], and 39% percent for the high-mid quartile compared to the high [HR = 1.39 (1.06 – 1.81), $p < 0.05$].

Because males were more likely than females to be married, and females were more likely than males to be widowed. Marital status accounts for some of the variance in the relationship between social integration and HF in males. When marital status (not married vs. married) was entered into the Cox regression model, not married males were 1.34 times more likely to develop HF over follow-up than married males [adjusted HR = 1.34 (1.04 – 1.73), $p < 0.05$]. The effect of adding this variable on the relationship between social integration and HF was minimal. Social integration was a significant independent predictor of incident HF (Wald statistic = 15.00, df = 3, $p < 0.01$) in a dose response fashion such that the risk of HF was 61% higher for males with social integration scores in the lowest quartile than for males with social integration scores in the highest quartile the sample [HR = 1.61 (1.24 – 2.09), $p < 0.001$], 53% percent higher for the low-mid quartile compared to the high [HR = 1.53 (1.16 – 2.00), $p < 0.01$], and 36% percent for the high-mid quartile compared to the high [HR = 1.36 (1.04 – 1.78), $p < 0.05$].

Perceived functional social support was not a significant predictor of heart failure above and beyond traditional risk factors in the sample or in male and female sub-samples.

Specific Aim 2: Social support and inflammatory markers and traditional risk factors for HF

The second aim of Study I was to examine the association between social support measures and inflammatory markers IL-6 and CRP. Secondarily, the associations between social support measures and traditional risk factors for HF were examined.

Social support and inflammatory markers. As expected, total social integration scores and total perceived social support scores were significantly positively correlated with each other ($r = 0.33$, $p < 0.001$). Levels of inflammatory markers IL-6 and CRP were also correlated ($r = 0.51$, $p < 0.001$). Both social integration and perceived social support scores were modestly negatively correlated with IL-6 (social integration $r = -0.05$, $p < 0.01$; perceived social support $r = -0.03$, $p < 0.05$). However, there was no relationship between either social support measure and CRP (social integration $r = -0.005$, p = NS; perceived social support $r = 0.001$, p = NS).

When an ANOVA was conducted examining the relationship between social integration quartiles and IL-6, the overall model was not significant ($F_{3, 4298} = 1.46$, p = NS). Post-hoc tests were conducted to test the hypothesis that those in the highest quartile of social integration would have significantly lower IL-6 than those in the lowest quartile of social integration. Results of post-hoc analyses partially supported this hypothesis, indicating that those in the lowest quartile of social integration tended to have the higher IL-6 levels than each of the three other quartiles (p's = 0.08-0.09). The ANOVA examining the relationship between perceived social support quartiles and IL-6 was marginally significant ($F_{3, 4811} = 2.57$, $p = 0.05$) and post-hoc tests indicated that those in the lowest quartile of social integration had significantly higher

levels of IL-6 than all other groups ($p < 0.05$ for each). Neither ANOVA examining social integration or perceived social support quartiles and CRP were significant.

Social integration and inflammatory markers: Gender differences. The correlation between social integration and perceived social support was the same among male and female sub-groups as was found for the entire sample ($r = 0.33$, $p < 0.001$). The correlation between IL-6 and CRP was 0.52 in females in 0.53 in males ($p < 0.001$ for each).

Table 5: Correlations between social support scores and inflammatory markers in CHS

	IL-6		**CRP**	
	Males	**Females**	**Males**	**Females**
Social integration	-0.05 *	-0.04 ^{m}	-0.01	-0.004
Perceived social support	-0.05 *	-0.01	0.02	-0.02

* $p < 0.05$, ^{m} $p < 0.10$

As shown in Table 5, in males, the correlations between IL-6 and social integration ($r = -0.05$, $p < 0.05$) and IL-6 and perceived social support ($r = -0.05$, $p < 0.05$) were both significant. In females, the correlation between social integration and IL-6 was marginally significant ($r = -0.04$, $p = 0.063$) and there was no relationship between perceived social support and IL-6 in females. There was no relationship between either social support measure and CRP in either sub-sample. When an ANOVA was conducted examining the relationship between social integration quartiles and IL-6, the overall model was not significant in males ($F_{3, 1752} = 1.43$, $p = NS$) or females ($F_{3, 2542} = 0.71$, $p = NS$). To test the hypothesis that males or females in the highest quartile of social integration would have significantly lower IL-6 than males or females in the

lowest quartile of social integration, post-hoc tests indicated that males in the lowest quartile of social integration had significantly higher IL-6 levels than the males in the mid-low quartiles ($p < 0.05$). There was no relationship between social integration and IL-6 in females.

When an ANOVA was conducted examining the relationship between perceived social support quartiles and IL-6 within each gender, the overall model was not significant in males ($F_{3, 1997} = 2.05$, p = NS). To test the hypothesis that males in the highest quartile of perceived social support would have significantly lower IL-6 than males in the lowest quartile of social integration, post-hoc tests confirmed this hypothesis ($p < 0.05$). Post-hoc tests also revealed that males in the lowest quartile of perceived social support tended to have higher levels of IL-6 than males in the mid-low quartile ($p = 0.05$). The relationship between perceived social support quartiles and IL-6 was not present in females.

Neither ANOVA examining social integration or perceived social support quartiles and CRP were significant among males or females.

Summary: A relationship between social integration and IL-6 and perceived social support and IL-6 was found in elderly males only. CRP was not related to social support in either gender.

Social integration and traditional risk factors for HF. Because social integration quartiles, but not perceived social support quartiles, predicted incident heart failure, secondary analyses compared individuals in the highest and lowest quartiles of social integration on the established socio-demographic, lifestyle, and medical risk factors for HF.

Socio-demographic factors: There was a greater proportion of older individuals in the lowest social integration quartile than expected and a lesser proportion of older individuals in the highest social integration quartile ($X_2 = 51.20$, df = 3, $p < 0.001$). There was a greater likelihood for African Americans to be in the lowest social integration quartile than the highest, while Caucasians were more likely to be in the highest social integration quartile than the lowest ($X_2 = 8.74$, df = 2, $p < 0.05$). See Table 6.

Table 6: Relationship between social integration and socio-demographic risk factors for HF

	Lowest SSN quartile	Highest SSN quartile	Statistic (t or X_2)	df	p
Over age 83	7.7%	3.1%	51.20	3	$p < 0.001$
African American race	16.8%	14.5%	8.74	2	$p < 0.05$

Lifestyle factors: Within the lowest quartile of social integration, there was a tendency for more individuals to smoke than expected, and within the highest quartile of social integration, there was tendency for fewer individuals to smoke than expected ($X_2 = 2.76$, df = 1, $p = 0.09$). Individuals in the highest quartile of social integration had a significantly higher BMI than those in the lowest quartile (27.1 kg/m^2 vs. 26.1 kg/m^2, $t = 5.90$, df = 2298, $p < 0.001$). See Table 7.

Table 7: Relationship between social integration and lifestyle risk factors for HF

	Lowest SSN quartile	Highest SSN quartile	Statistic (t or X_2)	df	p
Smoker	55.7%	52.3%	2.76	1	$p < 0.10$
BMI	26.1 kg/m^2	27.1 kg/m^2	5.90	2,298	$p < 0.001$

Medical factors: There was no relationship between social integration and hypertension or coronary disease at baseline, however, within the lowest quartile of social integration, there was a lesser likelihood of having diabetes and within the highest quartile, there was a greater likelihood of having diabetes (X_2 = 4.38, df = 1, $p < 0.05$). See Table 8.

Table 8: Relationship between social integration and medical risk factors for HF

	Lowest SSN quartile	Highest SSN quartile	Statistic (t or X_2)	df	p
CHD present	17.8%	18.0%	0.20	1	NS
Hypertension present	59.8%	56.7%	2.39	1	NS
Diabetes present	14.0%	17.2%	4.38	1	$p < 0.05$

Summary: Social integration tended to be related to socio-demographic and lifestyle risk factors for HF, but not medical risk factors.

Gender differences in the relationship of social integration and traditional risk factors

Socio-demographic factors: In both the male and female sample, there was a greater proportion of older individuals in the lowest social integration quartile than expected and a lesser proportion of older individuals in the highest social integration quartile (males: X_2 = 12.55, df = 3, $p < 0.01$; females: X_2 = 42.00, df = 3, $p < 0.001$). Although there was no association between social integration and race in males, there was a greater likelihood for African American females to be in the lowest social integration quartile than the highest, while Caucasian females were more likely to be in the highest social integration quartile than the lowest (X_2 = 8.12, df = 2, $p < 0.05$).

Lifestyle factors: Social integration was not associated with smoking in males or females. Males and females in the highest quartile of social integration had a significantly higher BMI than those in the lowest quartile (males: 26.9 kg/m^2 vs. 26.1 kg/m^2, t = 3.63, df = 978, $p < 0.001$; females: 27.2 kg/m^2 vs. 26.1 kg/m^2, t = 4.61, df = 1384, $p < 0.001$).

Medical factors: There was no relationship between social integration and hypertension or coronary disease at baseline in males for females. Social integration was associated with diabetes in males only. Males in within the lowest quartile of social integration were less likely to have diabetes than expected ($X_2 = 10.23$, df = 1, $p < 0.001$).

Summary: There were few gender differences in the relationship of social integration to traditional risk factors for HF. Specifically, diabetes was related to social integration in elderly males, but not females, and race was related to social integration in elderly females, but not males.

Specific Aim 3: Mediator analyses of the relationship between social integration and HF

Inflammatory marker mediators. As previously reported, social integration quartiles (but not perceived social support) predicted incident heart failure in males only (Wald statistic = 7.91, df = 3, $p < 0.05$), in a dose response fashion. Specific aim 3 of Study I was to determine if levels of inflammatory markers IL-6 and CRP might mediate this relationship. Cox regression analyses indicated that levels of IL-6 and CRP both predicted incident HF in the male sub-sample (IL-6: Wald statistic = 18.38, df = 1, $p < 0.001$; CRP: Wald statistic = 28.41, df = 1, $p < 0.001$), thus both inflammatory markers are possible candidate mediators of the relationship between social integration and incident HF. As previously reported, in males, the correlation between social

integration and CRP was not significant, thus CRP is eliminated as a potential mediator candidate. Also as previously reported, in males, the correlation between social integration and IL-6 was significant ($r = -0.05$, $p < 0.05$). However, as reported previously, the overall ANOVA model examining the relationship between social integration quartiles and IL-6 was not significant in males, even though post-hoc tests indicated that males in the lowest quartile of social integration had significantly higher IL-6 levels than the males in the mid-low quartiles ($p < 0.05$).

It remains possible that IL-6 is a weak, although unlikely, potential mediator of the relationship between social integration and HF. To test for mediation, one must enter the mediator candidate (IL-6) first into the model, and then enter the predictor variable (social integration) in the next block, in order to determine if the relationship between the predictor and the outcome still exists after accounting for the mediator variable. Following these steps, the Cox regression model indicated that a relationship between social integration and incident HF still existed, even after accounting for IL-6 (Wald statistic = 8.72, df = 3, $p < 0.05$). IL-6 was not a mediator of this relationship.

Other mediators. Additional possible mediators of this relationship between social integration and incident HF in males were examined. Because the relationship was found independent of baseline age, race, coronary heart disease status, hypertensive status, diabetes status, smoking status, and body mass index, these socio-demographic, lifestyle, and medical factors were not considered as potential mediators. The following possible mediators were examined. General health status was coded from 1-5, with lower numbers indicating better

subjective health status. Rating of health compared to others was coded from 1-3, with level 1 = perception of health better than others, 2 = perception of the same health same as others, and 3 = perception of health worse than others. Depression, major life events, and physical activity were measured as continuous variables based total scores from questions derived from validated questionnaires.

Depression was assessed using the shortened, 10-item version of the CES-D scale (Radloff, 1977; Andersen, Marmegren, Carter, & Patrick, 1994). The CES-D is a self-reported measure of depressive symptoms experienced in the past week. Items are coded on a scale of 0 to 3 and focus on mood (5 items), level of irritability (1 item), energy level (2 items) and sleep (1 item). Higher total scores indicate higher levels of depressive symptoms. Andersen and colleagues (1994) indicate that a score of ≥10 on the shortened version of the CES-D is indicative of depression. In the male sub-sample, 90.6% had scores < 10, and 9.4% had scores ≥10.

Physical activity was obtained via a self-report questionnaire developed from McPhillips and colleagues (1989). Participants were asked whether they had engaged in 12 common leisure time activities, excluding chores or work, in the previous 2 weeks. Activities were graded as being of a high (e.g., swimming, hiking, aerobics, jogging, tennis, racquetball, walking >=4 mph), moderate (e.g., golfing, bowling, biking, exercise cycle, dancing, calisthenics, walking 2-3 mph), or low (e.g., walking <2 mph) intensity, as previously described by Siscovick and colleagues (1997). Total number of kilocalories spent doing physical activity was a continuous variable used as a marker of extent of physical activity.

In males, social integration was negatively correlated with general health status ($r = -0.05$, $p < 0.01$), rating of health compared to others ($r = -0.03$, $p < 0.05$), and depression ($r = -0.12$, $p < 0.001$). Social support was positively correlated with total kilocalories spent in physical activity ($r = 0.08$, $p < 0.001$) and major life events ($r = 0.06$, $p < 0.001$). In males, Cox regression analyses indicated that incident HF was predicted by general health status (Wald statistic = 28.85, df = 1, $p < 0.001$), rating of health compared to others (Wald statistic = 8.20, df = 1, $p < 0.01$), total kilocalories spent in physical activity (Wald statistic = 11.96, df = 1, $p < 0.001$), and depression (Wald statistic = 4.67, df = 1, $p < 0.05$), but not major life events, thus ruling out this latter variable as a possible mediator.

General health status. When general health status was entered first into the Cox regression model, social integration quartiles still predicted incident HF in males (Wald statistic = 8.61, df = 3, $p < 0.05$). General health status was not a mediator of the relationship between social integration.

Self-reported health status compared to others. When self-reported health status compared to others was entered first into the Cox regression model, social integration quartiles marginally predicted incident HF in males (Wald statistic = 7.38, df = 3, $p = 0.061$), indicating that self-reported health status compared to others was a partial mediator of the relationship between social integration and incident HF in elderly, community-dwelling males. After controlling for self-reported health status compared to others, the risk of HF was 44% higher for individuals with social integration scores in the lowest quartile than for individuals with social integration scores in the highest quartile the sample [HR = 1.44 (1.06 – 1.88), $p < 0.01$], 28% percent higher for the low-mid quartile compared to the high [HR = 1.28 (0.97 – 1.70), $p = 0.08$],

and 25% percent for the high-mid quartile compared to the high [HR = 1.25 (0.96 –1.64), p = 0.095].

Physical activity. When total number of kilocalories spent during physical activity was entered first into the Cox regression model, social integration quartiles still predicted incident HF in males (Wald statistic = 7.93, df = 3, $p < 0.05$). Physical activity was not a mediator of the relationship between social integration.

Depression. When depression was entered first into the Cox regression model, social integration quartiles marginally predicted incident HF in males (Wald statistic = 7.63, df = 3, p = 0.054), indicating that depression is a partial mediator of the relationship between social integration and incident HF in elderly, community-dwelling males. After controlling for depression, the risk of HF was 42% higher for individuals with social integration scores in the lowest quartile than for males with social integration scores in the highest quartile the sample [HR = 1.42 (1.10 –1.83), $p < 0.01$], 30% percent higher for the low-mid quartile compared to the high [HR = 1.30 (0.99 – 1.70), p = 0.055], and 21% percent for the high-mid quartile compared to the high [HR = 1.21 (0.94 – 1.57), p = NS].

Relative strength of mediators. In summary, although inflammatory markers IL-6 and CRP did not mediate the relationship between social integration and incident HF in males, depression levels and self-reported health status compared to others both partially mediated this relationship. When both factors were entered together in the first block of the Cox regression model to predict HF, self-reported health status compared to others (Wald statistic = 3.57, df = 1, p = 0.06) was stronger than depression (Wald statistic = 1.90, df = 1, p = NS). As in the previous mediator models, the effect of social integration quartiles on incident HF, after controlling for

self-reported health status compared to others and depression, was marginally significant (Wald statistic = 7.13, df = 3, p = 0.07).

Test of the buffering effect of social support. In the mediator analyses, depression was found to be an predictor of incident HF in males, independent of social integration quartiles [HR = 1.02 (1.01 – 1.05), $p < 0.05$]. To determine if social support buffered the effects of depression on HF, a social integration by depression term was created by multiplying each individual's total social integration score by his/her depression score. This term was added to the Cox regression mediator model, but was not a significant predictor of incident HF.

Summary of mediator analyses. In contrast to the hypothesis, inflammatory marker levels did not mediate the relationship between social integration and incident heart failure in males. Self-reported health status as compared to others and depression were both partial mediators of this relationship.

Study I: Discussion

Summary of findings

The aims of the present study were to determine whether a structural or functional social support measure was an independent predictor of incident heart failure in the community-dwelling elderly participants in the Cardiovascular Health Study, examine the relationship between social support and traditional established risk factors for HF, and explore potential mediators of a relationship between social support and HF if one should exist. Social integration, but not perceived social support, predicted incident HF, independent of traditional risk factors for HF. Gender-specific analyses revealed that this relationship was present among elderly males,

but not elderly females. In males, social integration was related to traditional risk factors for HF as expected, such as younger age. However, social integration was also associated with other HF risk factors in males in unexpected directions (e.g., higher BMI and a higher prevalence of diabetes). Contrary to our hypothesis, inflammatory markers did not mediate the relationship between social integration and HF. Self-reported health status compared to others and depression were found to be partial mediators of this relationship.

Social integration as an independent predictor of HF

Hypothesis 1 predicted that social integration, not functional social support, would be an independent predictor of incident HF in community-dwelling elderly CHS participants. This hypothesis was confirmed. One of the important findings of the present study is that lack of social integration, a structural measure of social support, was found to be an independent predictor of incident heart failure in this sample of elderly individuals. Lack of perceived social support, a functional measure of social support, was not related to HF. The risk of HF was 35% higher for individuals with social integration scores in the lowest quartile than for individuals with social integration scores in the highest quartile of the sample. These results are consistent with previous studies that found that structural measures of social support are associated with hard and soft outcomes in HF patients. For instance, in patients with HF, lack of social integration was associated with increased mortality (Murberg, 2004), being single was associated with re-hospitalization (Chin & Goldberg, 1997), and individuals with smaller social networks had higher risk of re-hospitalization, independent of functional measures of social support (Rodríguez Artalejo et al., 2006). In these previous studies, lack of social integration may have

been the consequence of the process of HF itself, a progressive disorder with high mortality. The present study is the first to prospectively show the importance of social integration in the development of incident HF. Although there are no studies to corroborate this finding, structural measures of social support have been reported to be associated with incident CHD (e.g., Eng et al., 2002; Vogt et al., 1992), the development of initial cardiac events such as MI (e.g., Orth-Gomer et al., 1993), and CHD-related mortality (e.g., House et al., 1982).

Mechanisms to explain the relationship between social integration and HF

Lack social integration may contribute to the development of incident HF through various potential mechanisms. Some of these mechanisms, with a focus on the role of inflammation, were tested in the present study and will be discussed in detail in the sections below. First, there is an established relationship between social support and *health behaviors* that may explain the relationship social integration and incident HF. Social integration may positively influence negative health behaviors that contribute to the development of HF, such as smoking and poor dietary habits, and/or increase the likelihood of positive health behaviors that serve as protective factors for HF, such as adherence to medical recommendations and exercise. For example, Hartel, Stieber, & Keil (1988) found that individuals with more social contacts were less likely to be smokers. In HF patients, a poor social network predicted less access to health services and poorer treatment compliance (Evangelista, Berg, & Dracup, 2001). The relationship between social integration and health behaviors has been explained using a "social control" theory, in which the mere presence of another person implicitly demands more socially acceptable health behaviors (Coyne & Bolger, 1990).

Second, there is also an established relationship between social support and *biological processes* that contribute to the development of HF. Mookadam and Arthur, (2004) emphasizes in his review that social integration has been associated with deleterious neuroendocrine responses, immune responses (see below), and hemodynamic responses after MI that contribute to morbidity and mortality. Human and animal studies have shown that social isolation, or a lack of social integration, is associated with activation of the autonomic nervous system (ANS; Knox & Uvnas-Moberg, 1998; Sapolsky, Alberts, & Altman, 1997; Stanton, Patterson, & Levine, 1985). Social isolation is also related to hypothalamic-pituitary-adrenal (HPA) axis dysregulation in rats (Sánchez, Aguado, Sánchez-Toscano, & Saphier, 1998; Sánchez, Aguado, Sánchez-Toscano, & Saphier, 1995) and monkeys (Shively, Laber-Laird, & Anton, 1997). Besides these direct pathophysiological changes caused by lack of social integration, small social networks or infrequent contact with one's social network may also indirectly affect the body's physiology. For instance, a large social network can buffer the ANS and HPA axis activation of stressful life events (Cohen and Willis, 1985). Knox and Uvnas-Moberg (1998) hypothesize that the release of oxytocin in particular, in response to social support, may reduce ANS and HPA dysregulation.

Third, the relationship between social integration and incident HF may be explained by an association with psychosocial risk factors related to the development and progression of HF. For instance, depression is an independent predictor of HF (Abramson et al., 2001; Williams et al., 2002) and prospective evidence indicates that small network size is a risk factor for the development and worsening of depression in the context of CHD (e.g., Horsten et al., 2000). Similarly, in population-based studies, social network is associated with better subjective health (Litwin, 1998) and better health-related quality of life (Achat et al., 1998; Michael, Colditz,

Coakley, & Kawachi, 1999; García, Banegsa, Pérez-Regadera, Cabrera, & Rodríguez-Artalejo, 2005). These psychological variables have been associated with lower mortality rates in community studies (Idler & Benyamini, 1997) and may account for the relationship between lack of social integration and incident HF found in the present study.

Why lack of social integration, but not lack of functional social support, was related to HF

In the present study, lack of social integration, but not lack of perceived social support, predicted incident HF in a sample of high-functioning, community dwelling elderly individuals. Social integration was measured by assessing quantitative aspects of social relationships, such as the number of family members spoken to over one month, the number of relatives a person feels close to, number of close friends and the frequency of contact with them in a month, and whether an individual lives alone or with other people. It is a composite measure of both social network size and social network participation, and it is not clear which factor, if any, is a more important contributor to the development of HF. The functional social support measure in CHS evaluated general feelings of companionship (e.g., agreement with the statement: when I am lonely, there several people I can talk to), instrumental support (e.g., if I were sick, I could easily find someone to help me with my daily chores), and emotional support (e.g., when I need suggestions on how to deal with a personal problem, I know someone I can turn to). These perceptions of the availability of functional social support were not related to incident HF in either males or females in the sample. Studies predicting mortality have shown that quantitative measures of social support are more significant than qualitative measures. Orth-Gomer and Unden (1990) suggest that this consistency may be caused, in part, by the over-reporting of very positive ratings that produce too little variation. The distributions of social support data from the present

study support this speculation. The standard deviation of social integration data for males and females was 7.0, while the standard deviations of perceived social support data were 2.8 and 2.7 respectively. It appears that the possible over-reporting of the availability of functional social support may have contributed to the lack of significant findings between perceived social support and incident HF in CHS. Future studies examining received social support or more objective measures of functional social support, instead or in addition to perceived social support, may help to clarify this hypothesis.

Gender specificity in the relationship between social integration and HF

Even though lack of social integration independently predicted the development of incident HF in the CHS sample, planned gender-specific secondary analyses indicated that this relationship was present in males only, such that the risk of HF was 60% higher for males with social integration scores in the lowest quartile than for males with social integration scores in the highest quartile the sample. The strength of lack of social integration as a predictor of HF in males was similar to that of established risk factors for HF for males in this sample (e.g., coronary disease and age) and higher than other traditional risk factors, including race, hypertension, diabetes, BMI, and smoking (when classified as either current/former smoker vs. not current/former smoker or current smoker vs. not current smoker). The gender-specific finding, although not directly hypothesized, is not surprising, especially given the fact that numerous studies examining social support and CHD have been focused solely on samples of men (e.g., "Men Born in 1933" by Vogt et al., 1992, Orth-Gomer et al., 1993) and a relationship was found between structural social support and CHD mortality in Finnish men, but not women (Kaplan et al., 1988). Once HF develops, research seems to suggest that women are more

vulnerable to the effects of functional social support (Krumholz et al., 1998), yet the results of the present study would suggest that lack of social integration in men, but not women, is one factor that predisposes them to developing incident HF.

There are a number of possible reasons for such gender differences in the relationship between lack of social integration and incident HF in men. Numerous studies suggest important differences between women and men regarding their roles in and the quality of their social relationships (e.g., Berkman, Vaccarino, & Seeman, 1993; Shumaker & Hill, 1991). For example, women are more likely to be caregivers than men (Kessler, McLeod, & Wethington, 1985). If it is true that men receive more attention and care from their social networks than the women (who tend to provide these forms of functional social support), men may be more likely than women to experience the benefits of social integration, that include a lower incidence of heart failure for those with a large social network and frequent contact with network members. In this study, poor social integration predicted incident HF in males, independent of marital status, suggesting that this structural social support variable does not account for the effects of social integration on incident HF in elderly, community dwelling males.

Women have been shown to have more conflicted or negative social relationships than men (Rook, 1984). Thus women who lack social integration may be avoiding stressful social interactions that might be damaging to health. Men who lack social integration, on the other hand, may be missing out on supportive, high-quality social interactions that could be health-protective. Unfortunately, in this study, social integration was measured by assessing quantitative aspects of social relationships and the quality of the specific social relationships in one's social network was not directly assessed. The perceived social support measure tapped into general

perceptions of overall availability of functional social support. Future studies should include measures of reciprocity of social support and conflict among network members to provide evidence for these theories posited to explain gender differences in the importance of social integration on the development of HF.

Structural and functional social support measures were related to IL-6

Hypothesis 2 predicted that social integration, but not perceived social support, would be associated with inflammatory markers IL-6 and CRP. This hypothesis was not confirmed. Another important finding of the present study is that both the structural measure of social support (social integration) and the functional measure of social support (perceived social support) were inversely associated with IL-6 levels ($r = -0.05$ and $r = -0.03$, respectively) in the CHS sample. Although the magnitude of these correlations are low and perhaps clinically not that important, this finding is consistent with previous literature linking structural measures of social support to IL-6. In a large, community-based sample, Lutgendorf and colleagues (2004) found that lack of religious attendance, a specific measure of social integration, was associated with lower IL-6 levels. Population studies often find statistically significant, but small, effect sizes. The relationship between religious attendance and IL-6 in the Lutgendorf study was small ($r = -0.10$), but larger than the correlations found in the present study. Similarly, in a much smaller sample of ovarian cancer patients, weaker social attachment/levels of social integration were associated with lower IL-6 (Costanzo et al., 2005).

As discussed above, social support may influence IL-6 through health behaviors and psychological disturbances. There is evidence from prospective studies that social integration is related to smoking cessation (Lindstrom & Isacsson, 2002; Roski, Schmid, & Lando, 1996) and

physical activity (Ford, Ahluwalia, & Galuska, 2000), which in turn have been associated with IL-6 levels (Bermudez, Rifai, Buring, Manson, & Ridker, 2002; Ridker et al., 2000). The relationship between social support and depression was discussed in the previous section, and elevated IL-6 levels have been associated with depression (Steptoe et al., 2001; Anisman & Merali, 2002; Tiemeier et al., 2003) and chronic stress (Lutgendorf, 1999; Kiecolt-Glaser et al., 2003).

Gender differences in the relationship between social support and IL-6

In planned, exploratory secondary analyses, gender differences were found in the relationships between social support and IL-6. In males, IL-6 was inversely associated with both structural (social integration) and functional (perceived social support) measures of social support, while in females, structural social support tended to be inversely related to IL-6 and perceived social support was not associated with IL-6. In contrast to our prediction in hypothesis 2, perceived social support was related to IL-6 in males. To our knowledge, this study is the first to document the relationship between functional social support and inflammation in a large, community-based sample and the first to specify the impact on elderly males in particular. There are various reasons for the lack of data to corroborate our findings. First, few population studies have included measures of both structural and functional social support. Even fewer studies that do allow the simultaneous examination of functional and structural social support variables do not measure inflammatory markers. For instance, The MacArthur Aging Study (Loucks, Berkman, Gruenewald, & Seeman, 2006) measured IL-6 and CRP and included a social integration measure, but not a perceived social support scale. Second, smaller studies examining perceived social support and inflammatory markers in specific populations may be

underpowered, resulting in non-statistically significant results and difficulty in getting the findings into the literature. The Framingham Study could be used to verify the perceived social support findings of the present study, given the availability of measures of both types of social support, various markers of inflammation, and a large sample size to ensure a sufficiently powered study. Consistent with the present findings, Loucks, Sullivan, D'Agostino and colleagues (2006) found that social networks are inversely associated with IL-6 in men and women in the Framingham Study, but the effects of functional social support on inflammation were not examined.

Compared to women, men had slightly, but significantly, lower functional social support scores. Yet its relationship with IL-6 was present in males, not females. The perceived availability or quality of social support offered by one's social network in times of need has a particularly important impact on inflammation in elderly men. This finding is especially interesting in light of the previous discussion of gender differences. Indeed, men appear to be more likely to experience the benefits of available functional social support, as indicated by lower IL-6 levels, while women do not. This may be because men assume the receiving role in many social relationships, while women do the providing of support. However, women had higher levels of perceived availability of social support compared to men. Although probably not a clinically significant difference, in times of needs, women felt they could obtain needed social support at least as much as men. This finding suggests that it may be the underlying mechanisms through which perceived social support influences biology that are gender-specific, instead of a unique impact of functional social support on the male gender. The physiological correlates of gender differences in the relationship between social support and inflammation have not been

studied. Additional research, possibly using The Framingham Study data, may provide one avenue to further our understanding of this gender-specific relationship.

Social integration was not associated with CRP

In contrast to our expectations outlined in hypothesis 2 and the previous literature, social integration was ***not*** associated with CRP in either males or females in the CHS sample. Analysis of diabetics in NHANES data suggests that those not attending religious services, a specific measure of social integration, had higher CRP levels than those who did (King, Mainous et al., 2002). Loucks, Berkman, Gruenewald, and Seeman (2006) even identified gender differences in the relationship between social integration and CRP, which were predicted in the present study. In the MacArthur Aging Study, males in the lowest quartile of social integration were more likely to have an "at-risk" CRP level than males in the highest quartile of social integration, independent of age, race/ethnicity, smoking, alcohol consumption, physical activity, BMI, CHD, chronic conditions, physical functioning, SES, and depression.

Neither the structural nor the functional social support measure was related to CRP in either males or females in the CHS sample. There are numerous explanations that may account for this discrepancy. Although individuals in both CHS and the MacArthur Aging Study were high-functioning, the MacArthur Aging study limited the age range of its participants to 70-79, while CHS included anyone over age 65 living in the community. Furthermore, the analysis of NHANES data was conducted specifically on those individuals with diabetes in the Survey. Not only are the NHANES participants younger than the CHS participants, but those included in the sub-analysis to examine social integration and CRP would be more likely to have altered

inflammatory levels due to their diabetes (Willerson, 2003). Further research on social integration and CRP in older individuals is warranted to clarify these disparate findings.

Social integration was related to risk factors for HF

As reported above, social integration was related to lower IL-6 levels, but not CRP, a downstream inflammatory marker that was found to be one of the three most important independent predictors of HF in the CHS sample (Gottdiener et al., 2000). Interestingly, in general, social integration tended to be related to established socio-demographic and lifestyle risk factors for HF, but not traditional medical risk factors, and not always in the expected direction. In both genders, social integration was related to younger age and higher BMI. The social resources that form the basis of social support, such as the availability of friends and family, are likely to decrease with age in both genders. In this study, there was a significantly lower percentage of older elderly (over age 83) in the highest quartile of social integration compared to the percentage of younger elderly (ages 65-70). Such a gradient suggests that having a large social network or being able to participate in that social network becomes increasing important with age, as the risk of developing HF also grows greater. This combination of risk and protection may have allowed the effect of social integration, but not functional social support, to become evident in this sample. Although one might not expect individuals in the highest quartile of social integration to have significantly higher BMIs than those in the lowest quartile, it is common to find that low, not high, BMI is associated with mortality in samples of individuals over age 65 (e.g., Luchsinger, Patel, Tang, Schupf, & Mayeux, 2008). Thus social

integration does appear to be associated with health-promoting behaviors that help promote healthy weight maintenance and possibly survival.

For females, social integration was associated with race. Caucasian females were more likely to fall in the highest quartile of social integration than African Americans, who were more likely to fall in the lowest. Race differences in the prevalence and progression of heart failure have been documented, including increased prevalence, earlier onset, and increased risk for hospitalization and mortality in African Americans (Ferdinand, 2007). Lack of social integration may contribute to these health disparities by impacting health behaviors, directly affecting the body's physiology, and/or through its association with psychosocial risk factors for HF. In males, diabetes was more prevalent in individuals in the highest quartile of social integration compared to the lowest. This finding was unexpected, and, combined with the lack of relationships found between social integration and other medical factors (including hypertension and coronary disease), suggests that social integration is not influencing the development of HF through the medical risk factors pathway of the model proposed in the introduction of this study. Social integration was also not related to smoking, thus it does not appear that social integration is influencing HF through the health behaviors pathway. The last pathway proposed in the model to link social integration to HF was inflammation. Given the relationship between social integration and IL-6 in males, it is possible that IL-6 could be a potential mechanism of action to explain how social integration may influence the development and progression of HF.

Mediators of the relationship between social integration and incident HF

Hypothesis 3 predicted that inflammatory markers IL-6 and CRP would mediate the relationship between social integration and incident HF. This hypothesis was not confirmed. One of the central research questions of the present study was whether inflammation might by a key mediator of the relationship between lack of social integration and HF found in males. Although CRP was a strong independent predictor of HF (Gottdiener et al., 2000), CRP was not related to social integration, thus it could not be a mediator of this relationship. IL-6 was related to social integration and predictive of HF, yet social integration predicted incident HF in males after controlling for IL-6, thus IL-6 was also not a mediator. Thus, social integration does not appear to be influencing HF through any of the three bio-behavioral pathways (medical, inflammation, behavior) proposed in the initial model.

In order to better understand additional mechanisms that may explain the relationship between social integration and HF in males, psychosocial risk factors measured in CHS were examined even though they were not proposed in the initial model. The role of physical activity, a health behavior, was also examined. Social integration was positively correlated with physical activity and found to be inversely associated with depression. Males with higher social integration scores also reported better general health status and rating their health as better than that of their peers. When these variables were tested in exploratory post-hoc analyses, two partial mediators of the relationship between lack of social integration and HF in males were found. The rating of health status compared to peers and depression levels both reduced the impact of social integration on HF such that social integration became only a marginally significant predictor of HF. A buffering effect, or a role for social integration in lessening the impact of depression on

incident HF, was not supported by post-hoc analyses. The identification of two psychosocial risk factors suggest that a new psychosocial pathway be added to the initially proposed model. Although this pathway does not entirely explain the effect of lack of social integration on HF in males, it seems to be the most promising avenue of research according to the findings of the present study. Further research is needed to examine the bio-behavioral relationships between depression and social support in the development and progression of HF. It is likely that these interactions will be found to be as complex as those identified in post-MI patients enrolled in the ENRICHD study (e.g., Lett et al., 2007; Skala et al., under review).

Study limitations and strengths

There are several limitations inherent in the present study. First, the social support measures chosen for inclusion in CHS were broad measures of structural and functional social support based solely on self-reported data. Detailed analyses of specific measures of social integration or perceived social support were not possible. Second, only two inflammatory markers (IL-6 and CRP) were measured in CHS. Although these measures are commonly used in large-scale epidemiological studies, additional measures of inflammation, such as TNF-α, which mimics the HF syndrome when expressed in high concentrations, may have provided additional insight into a possible mechanism through which lack of social integration may influence incident HF. Third, the CHS sample was composed of community-dwelling individuals who were relatively healthy and high functioning recruited from Health Care Financing Administration files at four sites (Sacramento County, CA, Washington County, MD, Forsyth County, NC, and Allegheny County, PA). Thus findings may not be generalizable to the entire

population of individuals throughout the country. CHS participants are likely to have adequate access to health care, therefore the sample is not representative of the poor and uninsured older adults, which further limits the generalizability of the findings. Furthermore, as is the case with many volunteer cohorts, the CHS sample has been found to be healthier and better educated than those who declined to be part of the study (Tell et al., 1993). A "healthy cohort" effect may be biasing the results of the present study.

Despite these limitations, the present study has numerous strengths. It is a large, community-based, epidemiological study with directed recruitment of minority participants to ensure a representative sample. Moreover, the participants were followed for up to 17 years, allowing ample time for the development of the outcome of interest. Heart failure was the primary outcome in CHS and its presence or absence was carefully determined through medical record examination by the CHS Events Committee for diagnosis and treatment of HF, as well as symptoms, signs, and chest x-ray (Gottdiener et al., 2000). Many self-reported medical variables, such as history of coronary disease for example, were verified in the process of a medical records evaluation and modified if evidence of previous coronary disease was confirmed. Finally, both structural social support and functional social support measures were available for analysis of their comparative importance in the development of HF.

Study II: Clinical Study

Introduction

Given the relationship between lack of social integration and incident HF in males, further research is needed to delineate the specific aspects of lack of social integration (e.g., low number of social contacts vs. lack of participation in one's social network) that play an important role in the development and maintenance of HF. Clinical studies examining these specific aspects in populations at-risk for HF would be important. Furthermore, additional examination and clarification of the bio-behavioral mechanisms that underlie the relationship between social support and HF is warranted. An examination of physiological mechanisms in a sample at-risk for HF may provide additional insight into the actions of social support on HF development and progression.

As reported previously, Study I was limited by the specific broad measures of social support chosen for the epidemiological Cardiovascular Health Study, the availability of only two inflammatory markers (CRP and IL-6), and an assessment of social support and inflammation in a relatively healthy, community-dwelling population. Study II permitted an in-depth examination of various sub-domains of structural social support (e.g., total network size, number of embedded social networks) and functional social support (e.g., perceived emotional and instrumental social support). Furthermore, Study II assessed circulating inflammatory markers that include TNF-α, which mimics the HF syndrome when expressed in high concentrations, in a group of hospitalized individuals who are at-risk for HF because they have suffered an acute coronary syndrome (myocardial infarction or unstable angina).

Study II: Specific Aims and Hypotheses

The specific aims of Study II were:

1. To examine the inter-relationships among sub-domains of functional social support and sub-domains of social integration in a population of patients hospitalized for acute coronary syndrome (myocardial infarction or unstable angina).
2. To determine the association between each social support measure and levels of each inflammatory marker of HF (TNF-α, IL-6, and CRP) and the independent association of each type of social support (structural or functional) controlling for the other.
3. To specify which measures of social support, or combination of measures, best predicts each inflammatory marker (TNF-α, IL-6, and CRP) level.

The hypotheses of Study II were:

1. Functional social support measures (ISEL-12 tangible subscale, ISEL-12 appraisal subscale, ISEL-12 belonging subscale) will be positively associated with structural social support measures (marital status, living status, SNI network size, SNI embedded networks, and SNI network diversity, number of visitors, and hours visited). **Rationale:** Functional and structural social support measures are believed to represent similar underlying constructs in healthy and diseased populations, but each is also thought to represent a unique contribution to the broad definition of social support (Cohen, Underwood, & Gottlieb, 2000).
2. (a) The functional social support measures (ISEL appraisal, belonging, and tangible sub-scales) will be negatively associated with TNF-α, IL-6, and CRP inflammatory marker levels. **Rationale:** The relationship between measures of social support and inflammatory

markers has not been studied in cardiac populations, however data from Gidron and colleagues (2003) suggest that emotional support is negatively correlated with percentage of monocytes, a marker of inflammation and pre-cursor of the cytokine cascade, within 2 to 4 days of hospitalization for ACS. Depression is also negatively associated with TNF-α levels in patients with HF. The cytokine cascade, in which TNF-α stimulates production of IL-6, which produces increased levels of CRP, suggests that these relationships would hold for the markers of inflammation that will be measured in the present study. (b) This relationship will be independent of structural social support measures. **Rationale:** Some researchers (e.g., Lett et al., 2005; Seeman, 1996) argue that the quality, or function, of the social support is more important than the quantity, or structure. This may be particular true in stressful situations, such as during hospitalization for ACS, the population of focus for the present study.

3. Certain functional social support measures (belonging social support and appraisal social support) will best predict TNF-α, IL-6, and CRP levels. **Rationale:** Belonging and appraisal social support can be conceptualized as forms of emotional social support, which was most strongly negatively correlated to percentage of monocytes within a few days of ACS (Gidron, Armon, Gilutz, & Huleihel, 2003).

Study II: Methods

Sample

The sample consisted of consecutive consenting individuals admitted to the coronary intensive care unit or the progressive care unit of Johns Hopkins Bayview Medical Center for

chest pain, shortness of breath, or a diagnosis of acute coronary syndrome (ACS), including myocardial infarction (MI), unspecified angina, and unstable angina. Individuals whose symptoms or MI were due to cocaine or other drug use were excluded from the sample. Restricting the sample to only those who have not taken aspirin or heparin or other medications that may influence inflammatory markers would have made recruitment impossible in this clinical setting. Therefore, there were no exclusion criteria based on medications. Medications and dosages were recorded for post-hoc data analyses and examination. All individuals were cognitively able to consent within two days of being admitted to the hospital, and well enough to communicate the answers to the psychosocial questionnaires.

The study team cardiologists reviewed the electronic medical records, and paper medical records when necessary, at the end of the study enrollment period to verify the presence of coronary artery disease and confirm an acute coronary syndrome diagnosis for all recruited patients.

Independent Measures

Demographic, medical, and medical history

Patient information data collection sheet. Data were obtained from the patient's electronic medical record and/or self-report concerning the presenting complaint, current medications/drugs, and the presence of myocardial infarction. If myocardial infarction was present, the presence of ST-segment elevation was indicated, as well peak troponin I levels prior to enrollment to indicate the size of the infarction. History of coronary artery disease, hypertension, diabetes, and dyslipidemia were recorded from the medical record and/or self-

report. BMI and current and past smoking status were also obtained from the electronic medical record. (See Appendix A.)

Psychosocial Questionnaires

Perceived Functional Social Support. The Interpersonal Support Evaluation List short version (ISEL-12; Cohen & Hoberman, 1983) consists of a list of 12 statements concerning the perceived availability of potential social resources. The items are counterbalanced for desirability. Half the items are positive statements about social relationships and half are negative statements. The ISEL-12 was shortened from the 40-item version ISEL (Cohen & Hoberman, 1983) and designed to assess the perceived availability of three separate functions of social support as well as providing an overall support measure. The items which comprise the ISEL-12 fall into three 4-item subscales. The "tangible" subscale is intended to measure perceived availability of material aid; the "appraisal" subscale, the perceived availability of someone to talk to about one's problems; and the "belonging" subscale, the perceived availability of people one can do things with. The ISEL has been used widely in health-related research. For the 40-version scale, alpha and test-retest reliability are approximately 0.90. For the sub-scales, internal consistency and test-retest reliabilities range from 0.70 to 0.80 and they are moderately inter-correlated (Cohen & Hoberman, 1983).

Social Integration. The Social Network Index (SNI; adapted from Cohen et al., 1997) assesses the number of people respondents see or talk to on a regular basis, including family, friends, colleagues, and neighbors. The SNI measures the number of high-contact roles (network diversity; separate social roles that the respondent takes on), number of people in one’s social

network (total number of people with whom the respondent has regular contact, i.e., at least once every two weeks), and number of embedded networks (different network domains in which the respondent is active). The SNI was used by Cohen and colleagues (1997) in a study of college students' susceptibility to the common cold. Network diversity, but not total number of network members was found to be inversely related to the rate of colds. Additional questions will be asked regarding marital status, living status (alone, with spouse, with family, with friend, with professional caregiver, etc.), number of people living in the household, total number of visitors to date, and total number of minutes or hours visitors accompanied the patient during their stay.

Loneliness. Due to patient burden, a short, three-item form of the R-UCLA Loneliness Scale (Russell, Peplau, & Ferguson, 1978) was be used (Russell, Peplau, & Cutrona, 1980). Participants were asked to respond to three questions about how often they lack companionship, feel left out, and feel isolated from others. They chose between hardly ever, sometimes, and often responses. The original 20-item scale has good reliability ($\alpha = 0.94$) and acceptable validity (Russell, Peplau, & Ferguson, 1978; Perlman & Peplau, 1981). The sum of the three items reflects the respondent's loneliness score, with higher scores indicating more loneliness.

State Anxiety. The Spielberger State Anxiety Inventory (SAI; Spielberger et al., 1983) consists of 20 items and asks respondents to describe their current feelings by answering each item using a 4-point Likert-type scale with 1 representing not at all and 4 indicating very much so. Ten of items expressive negative affect states, like confused, jittery, and indecisive. The other 10 items express positive conditions, including secure, at ease, relaxed. Positive affect items are reverse scored and the ratings are summed to produce a total state anxiety score. Scores range from 20 to 80 and the higher the score the greater the level of self-reported state anxiety. The

SAI has well-established reliability and validity with many populations, including patients with ACS (Frazier et al., 2002; Crowe, Runions, Ebbesen, Oldridge, & Streiner, 1996; Frasure-Smith, Lesperance, & Talajic, 1995).

Depression. The 9-question Primary Care Evaluation of Mental Disorders Brief Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) is a self-report questionnaire used to assess depressive symptoms. For each of the 9 depressive symptoms, patients indicate whether, during the previous 2 weeks, the symptom had bothered them "not at all," "several days," "more than half the days," or "nearly every day," yielding a score of 0 to 3. The PHQ score ranges from 0 to 27. A cutoff of 10 points or higher corresponds to a level of at least moderate depression and represents the minimum number of symptoms required for a *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition (DSM-IV) diagnosis of major depression [American Psychiatric Association (APA), 1994]. This cutoff has 88% sensitivity and 88% specificity for major depression. The diagnostic validity of the PHQ is comparable to clinician-administered assessments and this questionnaire yields an index of depressive symptom severity (Spitzer, Kroenke, & Williams, 1999).

The Beck Depression Inventory Second Edition (BDI-II; Beck, Steer, & Brown, 1996) was also used to measure depression. The BDI-II is a 21-item self-report instrument that assesses the existence and severity of symptoms of depression as listed in the DSM-IV (APA, 1994). Each item corresponds to a symptom of depression and the respondent much choose a statement for each item that accurately reflects the past two weeks. Items are rated on a four point scale ranging from 0 to 3. Responses are summed to provide a total BDI score. Although cut score guidelines may vary depending on the characteristics of the sample, a total score of 0 – 13 is

considered minimal range, 14 – 19 is mild, 20 – 28 is moderate, and 29 – 63 is severe. The BDI has been used for 35 years to identify and assess depressive symptoms, and has been reported to be highly reliable regardless of the population. It has a high coefficient alpha (.92) and high test-retest reliability (r = .93). It is commonly used in studies of ACS patients (e.g., see Thombs et al., 2006 and Huffman et al., 2006).

Hopelessness. The Beck Hopelessness Scale (BHS; Beck, Weissman, Lester, & Trexler, 1974) is a 20-item scale that measures negative attitudes about the future. Respondents must decide if statements are true or false. Individual items are then summed to create a total score. A number of studies have analyzed the internal consistency and factor structure of the BHS. Inconsistent findings have fostered some debate regarding the validity of the scale, particularly in non-psychiatric samples (see Steed, 2001; Rosenfeld, Gibson, Kramer, & Breitbart, 2004). However, KR-20 coefficients (measures of the scale's internal consistency) are acceptable and range from 0.82 to 0.93. Test-retest reliability is also acceptable (r = 0.69).

Please see Appendix A for the patient information sheet and questionnaires.

Dependent Measures

Tumor necrosis factor-α (TNF-α) was measured by an ultra-sensitive, solid-phase sandwich ELISA using a monoclonal antibody specific for TNFα (Quantikine HS Human TNFα Immunoassay; R&D Systems, Minneapolis, MN). The detection range is 0.5 – 32 pg/mL (normal circulating levels are reported to be in the 10-80 pg/mL range).

Interleukin-6 (IL-6) was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). A monoclonal anti-IL6 antibody is coated on the plastic support and a polyclonal anti-IL6 antibody is used as the sandwich antibody. The amount of IL-6 bound is determined by a color reaction. The expected normal range per the manufacturer is 0.24-12.5 pg/mL.

C-reactive protein (CRP) was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). A monoclonal anti-CRP antibody is coated on the plastic support and a polyclonal anti-CRP antibody is used as the sandwich antibody. The amount of CRP bound is determined by a color reaction. The detection range is 0.175–1100 mg/L. Expected values for CRP in normal, healthy individuals are $\leq$3 mg/L.

Procedure

Patient recruitment. Patient recruitment occurred on weekdays between 6am and 12pm. As part of the study protocol, a HIPAA waiver from the Johns Hopkins Bayview Medical Center IRB was obtained that allowed research study coordinators to consult the Bayview Hospital electronic medical records system (Meditech) for the nursing census of individuals admitted to the coronary intensive care unit and progressive care unit on a given day. If an individual had been admitted within two days and the admitted individual presents with chest pain, shortness of breath, a diagnosis of ACS or MI, or a diagnosis to rule out MI or ACS, the individual's electronic medical record was consulted to determine if patient met inclusion criteria for the study. Specifically, the diagnosis was confirmed via the medical record primary diagnosis, elevated cardiac enzyme levels (e.g., troponin or CK), and/or confirmation by cardiac fellows on the floor, attending physician, or the study team cardiologists. The cardiac fellows on the floor

were consulted daily to establish any new potential participants that may have gone undetected via the above procedure (e.g., still in the emergency room, recent MI in a patient admitted for a different cause, etc.). If there was any doubt as to the eligibility of a given participant, the study team cardiologists were contacted for a consult. Determination was made via a thorough examination of the individual's medical chart on the floor that included symptom description notes, medical history data, and electrocardiograph readings, etc.

The resident on duty and the patient's nurse were consulted to ensure that the patient was cognitively aware and able to be consented. All patients meeting inclusion criteria were approached for informed consent if possible. Study II was an addendum to an on-going research study at Johns Hopkins University Bayview Hospital with these patients. (See initial IRB approval letter in Appendix B.) The addendum to the research protocol and new informed consent forms incorporating the Study II protocol were approved by the Human Subjects Committee of the Bayview IRB. (See Appendix C and D.) The IRB at Uniformed Services University of the Health Sciences also approved this study. (See Appendix E.)

Blood collection and storage. The cardiologist or phlebotomist used a 21-gauge butterfly needle to draw approximately 30 mL of blood at the patient's bedside between 9am and 12pm from all patients who consented on a particular day. Consistently drawing blood at this time helped to account for circadian rhythms that may have influenced the inflammatory markers under investigation. Blood samples were collected in vacuum tubes that each hold approximately 3 mL of blood. The first 4-5 mL of blood collected was discarded, in order to eliminate the immune activation as a result of the blood draw as a confounder in the present study. The following 15 mL were used for platelet aggregation analyses (conducted as part of the original

study protocol). The remaining 13mL of blood was collected in 3 mL vacuum tubes containing dry reagents (EDTA) and mixed by gently inverting the tube for 30 seconds. The tubes were immediately put on ice and kept on ice until separation of plasma could be performed. Tubes were centrifuged at 1000g for 15 minutes at 4° C. The resulting serum was aliquoted in 500 μL amounts and frozen in separate Eppendorf tubes at -80^{o} C until analysis. When recruitment ended and blood samples had been collected from all patients enrolled in the study, the plasma from all enrolled patients were assayed at the same time. All samples were labeled and processed in duplicate for quality assurance. The assays were performed at Johns Hopkins University in the laboratory of Gayle G. Page, DNSc, RN, FAAN.

Administration of questionnaires. The research coordinator will verbally administer the psychosocial questionnaires to the participant, unless the patient specifically requests completing the copies him/herself. Completing the questionnaires took 30 minutes to 1 hour and 15 minutes. To avoid patient fatigue, participants were offered a break after 30 minutes. The total time a patient committed to the study averaged 1 hour from beginning to end.

Study II: Data Analyses

Primary data analyses

For Specific Aim 1, inter-relationships among measures of perceived functional social support and measures of structural social support were obtained using correlational analyses with a Bonferroni correction to account for increased Type I error resulting from multiple analyses. If the data were not normally distributed, non-parametric Spearman's rho correlations were used. For Specific Aim 2, correlational analyses with Bonferroni correction were also used to establish

the associations between each social support measure and each inflammatory marker. Multiple linear regression analyses with Bonferroni correction were used to control for social support measures in order to determine the independent associations of different forms of social support. For Specific Aim 3, to specify which measure of social support, or combination of measures, was the strongest predictor of each inflammatory marker, three separate backward multivariate linear regressions were be conducted. All social support measures were entered into the linear regression in one step, and the computer chose those variables whose variance significantly accounted for the variance in TNF-α, IL-6, and CRP in this sample.

Secondary data analyses

Inter-relationships between social support and loneliness were examined and the importance of loneliness as a predictor of inflammatory marker levels was determined. If social support had not been found to be associated with inflammatory maker levels, the stress-buffering hypothesis would have been examined using state anxiety scores and/or the questions asking for a rating of distress as a result of the hospitalization as indicators of current stress levels. The impact of stress and social support on inflammatory marker levels would have then been tested, with expected statistical significance for the interaction term.

Study II: Power Analyses

Gidron and colleagues (2003) studied the relationship between emotional support assessed within 2 to 4 days of hospitalization for acute coronary syndrome and inflammatory markers (total leukocytes, and percentages of monocytes, neutrophils, and lymphocytes) measured upon admission. A correlation of r = -0.43 between emotional support and percentage

of monocytes was documented, as well as a partial correlation (controlling for left ventricular function and arrival time) of r = -0.47. These data suggested a sample size of 37 would have been necessary to detect a similar effect size at 80% power and α = 0.05. The relationship between depression and TNF-α in HF patients (Parissis et al., 2004) indicated a large effect size (r = 0.89). A sample size of 15 was deemed sufficient to detect an effect size of that magnitude at 98% power and α = 0.05. The relationship between depression and IL-6 in the same group of HF patients (r = 0.45) indicated that a sample size of 37 was sufficient to detect a similar effect size at 80% power and α = 0.05. Thus, a sample size of 37 ACS patients was expected to be sufficient to detect a moderate effect size of social support on inflammatory markers TNF-α, IL-6, and CRP at α = 0.05 and 80% power.

Study II: Results

Sample

Fifty three patients with acute coronary syndrome were recruited within two days of hospitalization in Johns Hopkins Bayview Cardiac Intensive Care and Progressive Care Units during 2007. See flow chart (Figure 5) for specifics as to the number of patients who met inclusion criteria and who were excluded. The baseline demographic, medical history, lifestyle, and medical/medication during hospitalization characteristics of the sample are presented in Table 9. In addition, the mean BDI depression score was 10.14 (SD = 10.33), with 71.1% (n = 32) with minimal depression, 15.6% (n = 7) with mild depression, 6.7% (n = 3) with moderate depression, and 6.7% (n = 3) with severe depression range. The mean PHQ-9 depression score was 6.65 (SD = 6.80), with 73.9% (n = 34) scoring > 8 and indicating no mood disorder, 2.2%

(n = 1) scoring between 8 and 10 and indicating a possible mood disorder, and 23.9% scoring > 10 and indicating a probable mood disorder.

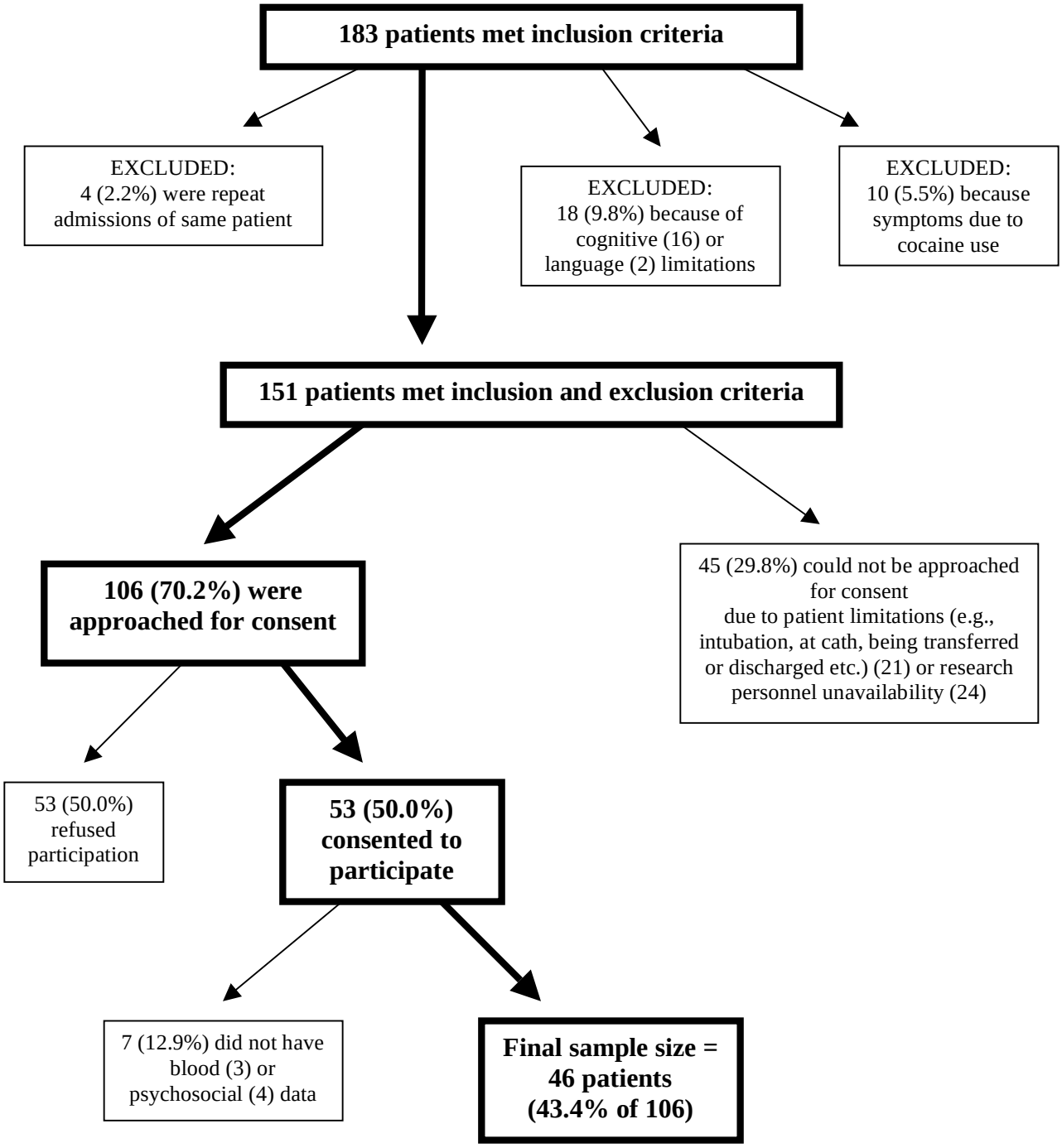

Figure 5: Patient recruitment flow chart

Table 9: Baseline characteristics of ACS sample (n = 46)

DEMOGRAPHICS	
Mean age	62.2 years (SD=14.0)
% of males in the sample	71.7%
Race:	
Caucasian	84.8%
African American	13.0%
Other (Hispanic)	2.2%
Marital status:	
Married	47.8%
Divorced or separated	32.6%
Widowed	13.0%
Never married	6.5%
MEDICAL HISTORY	
Family history of CVD in men	50.0%
Family history of CVD in women	23.1%
History of hypertension	73.9%
History of high cholesterol	71.7%
History of diabetes	38.6%
Had prior myocardial infarction	41.3%
History of heart failure	21.7%
History of depression and/or psychiatric disorder	15.2%
LIFESTYLE	
Current smoker	45.7%
Mean body mass index	29.9 kg/m^2 (SD=5.1)
MEDICAL/MEDICATION DURING HOSPITALIZATION	
Mean troponin I levels	26.0 (SD=44.0)
Aspirin Use 81 mg 162 mg 325 mg	95.7% 2.3% 40.9% 56.8%
Plavix Use	73.9%
Heparin Use	97.8%
WarfarinUse	4.3%
IIb/IIIa Blocker Use	52.2%
Statin Use	91.3%
Beta Blocker Use	93.5%
ACE/ARB Use	78.3%
Ca^{++} Channel Blocker Use	21.7%
Nitroglycerin Use	76.1%
Other NSAID Use	13.0%
Anti-Depressant Use	10.9%

Benzodiazepine Use	19.6%
Others	2.2%

The final sample (n = 46) was slightly younger than the larger sample who met inclusion and exclusion criteria (n = 151) who had a mean age of 66.02 (SD = 15.30). The one sample t-test comparing the sample age to the population age was marginally significant (t = -1.87, p = 0.068). The final sample (n = 46) was also slightly under-representative of eligible females (28.3% vs. 41.1%) and over-representative of eligible males (58.9% vs. 71.7%). The chi-square test was marginally significant (X^2 = 3.13, df = 1, p = 0.077). Data on race/ethnicity were not available on the larger sample of individuals who met inclusion and exclusion criteria.

Specific Aim 1: Inter-relationships between structural and functional social support in ACS

The first aim of Study II was to examine the inter-relationships among sub-domains of functional social support and sub-domains of social integration in a population of patients within two days of being hospitalized for acute coronary syndrome. Frequency data indicated that the functional social support data and two structural social support measures (number of people in household and number of hours patients received visitors) were not normally distributed. Non-parametric Spearman's correlations were used to test relationship with these variables.

Correlations among functional social support sub-scales. To account for possible type II error resulting from multiple analyses, Bonferroni correction was used and the α level was set at 0.02 (0.05/3). As expected and shown in Table 10, the three sub-scales of the ISEL perceived social support measure were highly correlated. The appraisal sub-scale was highly correlated with the belonging sub-scale (rho = 0.69, p < 0.001) and moderately with the tangible sub-scale

(rho = 0.47, $p < 0.01$), and the belonging sub-scale was moderately correlated with the tangible sub-scale (rho = 0.43, $p < 0.01$).

Table 10: Spearman's rho inter-correlations among ISEL sub-scales

	Appraisal	Belonging	Tangible
Appraisal	-	-	-
Belonging	0.69 ***	-	-
Tangible	0.47 **	0.43 **	-

*** $p < 0.001$, ** $p < 0.01$

Correlations among structural social support measures. To account for possible type II error resulting from multiple analyses, Bonferroni correction was used and the α level was set at 0.002 (0.05/21). The correlations among structural social support measures are shown in Table 11. As expected, the three measures of the Social Network Index, or social integration, were highly correlated. Total network size (total people in social network) was highly correlated with network diversity ($r = 0.57$, $p < 0.001$) and number of embedded networks ($r = 0.80$, $p < 0.001$). Network diversity was also highly correlated with number of embedded networks ($r = 0.75$, $p < 0.001$). The number of hours patients reported receiving visitors was significantly correlated with the total number of visitors during hospitalization (rho = 0.87, $p < 0.001$) and network diversity (rho = 0.47, $p < 0.002$). Number of individuals in the patient's household and the patient's marital status were not significantly associated with any structural measure of social support.

Table 11: Inter-correlations of structural measures of social support

	Network size	Network diversity	# of embedded networks	# of visitors	# of hours visited	# of people in household
Network size	-	-	-	-	-	-
Network diversity	0.57 ***	-	-	-	-	-
# of embedded networks	0.80 ***	0.75 ***	-	-	-	-
# of visitors	0.37 *	0.38 **	0.41 **	-		-
# of hours visited (rho)	0.38 *	0.47 **	0.38 *	0.87***	-	-
# of people in household (rho)	0.16	0.26	0.14	0.11	0.24	-

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Although many correlations between structural measures did not reach statistical significance at the Bonferroni-corrected alpha level set for these analyses, various moderate size correlations were found that did reach traditional significance levels in this small sample size. For instance, number of visitors during hospitalization was correlated with the three social network measures (network size: $r = 0.37$, $p < 0.05$; network diversity: $r = 0.38$, $p < 0.01$; number of embedded networks: $r = 0.41$, $p < 0.01$). Number of hours each patient reported receiving visitors was also correlated with two other social network questionnaire measures (network size: rho = 0.38, $p < 0.05$; number of embedded networks: rho = 0.38, $p < 0.05$). The magnitude of the correlations between number of individuals in the patient's household and structural social support measures and were small and did not reach traditional levels of significance. Presence or absence of children or grandchildren in the household was specifically examined using independent t-tests and the U-Mann Whitley non-parametric test for number of hours visited. Not surprising, patients living with a child and/or grandchild (n = 14) tended to have larger embedded networks than patients who didn't live with a child and/.or grandchild (n =

32) ($t = 1.77$, $df = 44$, $p = 0.084$). The relationship between the patient's marital status and structural social support variables was tested using independent t-tests for all variables, except number of individuals in the patient's household and number of hours the patient reported receiving visitors. For these non-normally distributed variables, U-Mann Whitley non-parametric analyses were used. Martial status was not associated with any structural social support measure.

Table 12: Spearman's rho correlations between structural and functional measures of social support

	Appraisal	Belonging	Tangible
Network size	0.18	0.29	0.22
Network diversity	0.22	0.10	0.29
# of embedded networks	0.18	0.24	0.22
# of visitors	0.27	0.21	0.29
# of hours visited	0.32 *	0.44 **	0.40 *
# of people in household	0.00	-0.10	0.06

** $p < 0.01$, * $p < 0.05$

Inter-relationships between structural and functional social support. To account for possible type II error resulting from multiple analyses, Bonferroni correction was used and the α level was set at 0.002 (0.05/21). In this group of hospitalized ACS patients, no statistically significant Spearman's rho correlations were found between structural and functional social support measures with the stringent Bonferroni-corrected alpha level set for these analyses. See Table 12. The relationship between the patient's marital status and functional social support variables, as tested by U-Mann Whitley non-parametric analyses, were not significant. Nor were the relationships between presence or absence of a child and/or grandchild in the household and functional social support. However, the correlations between the number of hours patients reported being accompanied by visitors during their hospital stay and all functional measures of

social support were found to be moderate in size and met traditional significance levels (appraisal: rho = 0.32, $p < 0.05$; belonging: rho = 0.44, $p < 0.01$; tangible: rho = 0.40, $p < 0.05$).

In summary, although functional measures of structural support and structural measures of social support were significantly correlated within their respective areas, only one the structural measure (the number of hours the patient reported being accompanied by visitors) showed a moderate size correlation with functional measures of social support.

Specific Aim 2: Social support and inflammatory markers in ACS

The second aim of Study II was to determine the association between each social support measure and levels of each of three inflammatory markers (TNF-α, IL-6, and CRP). Further analyses then examined the independent association of each type of social support (structural or functional) on inflammatory markers, controlling for the other.

Table 13: Spearman's rho correlations between functional social support measures and inflammatory markers

	TNF-α	IL-6	CRP
Appraisal	-0.14	-0.23	-0.19
Belonging	-0.14	-0.16	-0.32 *
Tangible	-0.09	-0.30 *	-0.06

* $p < 0.05$

Functional social support and inflammatory markers. To account for possible type II error resulting from multiple analyses, Bonferroni correction was used and the α level was set at 0.005 (0.05/9). No statistically significant Spearman's rho correlations were found between

functional social support measures and inflammatory markers IL-6, TNF-α, or CRP with the stringent Bonferroni-corrected alpha level set for these analyses. See Table 13. However, the negative correlation between the belonging sub-scale and CRP was moderate in size (rho = -0.32, $p < 0.05$). Similarly, the negative correlation between the tangible sub-scale and IL-6 was moderate in size (rho = -0.30, $p < 0.05$).

Table 14: Correlations between structural social support measures and inflammatory markers

	TNF-α	IL-6	CRP
Network size	0.01	-0.04	-0.15
Network diversity	-0.07	-0.27	-0.17
# of embedded networks	0.00	-0.12	-0.16
# of visitors	-0.04	-0.10	-0.11
# of hours visited (rho)	-0.06	-0.20	-0.30
# of people in household (rho)	-0.27	-0.31 *	-0.09

* $p < 0.05$

Structural social support and inflammatory markers. To account for possible type II error resulting from multiple analyses, Bonferroni correction was used and the α level was set at 0.002 (0.05/21). No statistically significant correlations were found between structural measures of social support measures and inflammatory markers IL-6, TNF-α, or CRP with the stringent Bonferroni-corrected alpha level set for these analyses. See Table 14. However, the negative correlation between number of people in the patient's household and IL-6 was moderate in size and reached traditional levels of significance (rho = -0.31, $p < 0.05$). Presence or absence of a child and/or grandchild in the household was not related to any inflammatory marker.

Inflammatory variables were log-transformed to make them normally distributed and their relationship with martial status was tested using a Multivariate Analysis of the Variance

(MANOVA). The overall F for the model reached traditional significance levels ($F_{1,44} = 3.07$, $p < 0.05$), and the relationships between marital status and two inflammatory markers (TNF-α and IL-6) also reached traditional levels of significance. Compared to patients who were separated, divorced, widowed, or never married/living in a marital-like relationship, patients who were married or living in a marital-like relationship had lower levels of TNF-α ($F_{1,44} = 7.54$, $p < 0.01$) and IL-6 ($F_{1,44} = 4.81$, $p < 0.05$).

Functional vs. structural social support and inflammatory markers. To determine the relative strength of functional vs. structural social support on inflammatory markers, all social support measures that were individually related to each inflammatory marker at traditional levels of significance were entered simultaneously into separate regression models predicting IL-6, TNF-α, and CRP.

Social support and IL-6. The functional social support measure the ISEL tangible sub-scale and two structural social support measures, the number of people in household and martial status, were associated with IL-6 in univariate analyses. When these three variables were entered into a regression model to predict IL-6, the factors explained 20.5% of the variance and the overall regression model was significant ($F_{3,41} = 3.52$, $p < 0.05$). Number of people in the household was found to predict IL-6 levels, independent of tangible social support and marital status ($\beta = -0.25$, $t = 2.02$, $p < 0.05$).

Social support and TNF-α. Marital status was the only functional or structural variable to be significantly associated with TNF-α, thus the regression analysis for this outcome was not

necessary. Marital status, a structural measure of social support, is the strongest relative predictor of TNF-α in this sample.

Social support and CRP. The ISEL belonging sub-scale was the only functional or structural variables to be significantly associated with CRP, thus the regression analysis for this outcome was not necessary. Belonging, a functional measure of social support, is the strongest relative predictor of CRP in this sample.

In summary, using the stringent Bonferroni-corrected alpha levels, there were no statistically significant relationships between inflammatory marker levels and either functional or structural social support measures. Using traditional significance levels, marital status was the strongest relative predictor of TNF-α, while belonging was the strongest relative predictor of CRP. Number of people in the patient's household significantly predicted IL-6 in this sample, above and beyond tangible social support and marital status, which were significantly related to IL-6 in univariate analyses.

Specific Aim 3: Comparing social support predictors of inflammatory markers in ACS

The second part of the second aim of Study II, as described above, examined the independent contributions of each type of social support to inflammation. The third aim of Study II was to specify which measures, of all measured social support constructs or combination of constructs, were the strongest predictors of each inflammatory marker (TNF-α, IL-6, and CRP) level in hospitalized ACS patients. The univariate relationships between the variables and the inflammatory marker were irrelevant in this new set of analyses. Backwards linear regression

modeling for IL-6 indicated that the combination of the ISEL appraisal sub-scale ($\beta = -0.10$, $t = 2.78$, $p < 0.01$) and the number of individuals in the patient's household ($\beta = -0.33$, $t = 2.89$, $p < 0.01$) was the strongest predictor of IL-6 levels. For TNF-α, marital status ($\beta = -0.50$, $t = 2.60$, $p < 0.05$) was the strongest predictor. None of the structural or functional social support variables were considered to be good predictors of CRP according to the backwards linear regression model results.

In summary, as found previously, number of individuals in the patient's household is a strong predictor of IL-6. These analyses suggest that the functional social support measure of appraisal is an equally important construct in predicting IL-6 levels in this group of ACS patients. The structural measure marital status, as indicated by the previous aim's comparison, is the strongest predictor of TNF-α. In contrast, no functional or structural social support measure appears to be a strong predictor of CRP.

Secondary Analyses: Loneliness and its relationship to social support and inflammatory markers

In exploratory analyses, the relationship of loneliness to functional and structural social support measures was examined. The R-UCLA total loneliness score data were not normally distributed, so non-parametric Spearman's rho correlations were used. Loneliness was significantly negatively correlated with the functional measures of social support (appraisal: rho = -0.37, $p < 0.05$; belonging: rho = -0.49, $p < 0.01$; tangible: rho = -0.31, $p < 0.05$). The only structural measure of social support correlated with loneliness was number of embedded networks (rho = -0.32, $p < 0.05$). In further analyses, the relationship between loneliness and

each inflammatory marker levels was examined. Loneliness was not associated with TNF-α, IL-6, or CRP levels in this sample of ACS patients within 2 days of hospitalization.

Study II: Discussion

Summary of findings

The aims of Study II were to examine the inter-relationships between measures of functional and structural social support in a group of patients within 2 days of hospitalization for ACS and determine the social support measures, or combination of measures, that were the strongest predictors of three inflammatory markers: TNF-α, IL-6, and CRP. We found that, although functional and structural social support measures were inter-correlated within functional and structural domains respectively, the only structural variable that was associated with functional social support variables was the number of hours the patient reported being accompanied by visitors during their hospital stay. In the present study, marital status was the strongest relative predictor of TNF-α, belonging was the strongest relative predictor of CRP, and number of people in the patient's household significantly predicted IL-6 in this sample, above and beyond tangible social support and marital status, which were significantly related to IL-6 in univariate analyses.

Inter-relationship within functional and structural social support measures

Although not a study hypothesis, inter-relationships within functional and structural social support measures were examined. Not surprisingly, the sub-domains of functional social support measured by the ISEL were significantly and moderately to highly inter-correlated, with

rho's ranging from 0.43 to 0.69. Also as one would expect, the structural social support measures of the Social Network Index (SNI network size, SNI network diversity, and SNI number of embedded networks) were highly inter-correlated, with r's ranging from 0.57 to 0.80. The number of hours the patient reported being accompanied by visitors was a surprisingly informative measure. Time receiving visitors was significantly and moderately correlated with network diversity, or the number of high contact separate social roles. The correlations between the other SNI variables (social network size and number of embedded networks) and number of visitors and number of hours were also significant. These relationships among structural social support measures in hospitalized ACS patients within two days of admission may indicate that, when the social network members determine that a person is in need of functional social support (during an unexpected health problem and subsequent hospital stay), the person's social network is activated and those network members with whom the patient has frequent contact are likely to visit and stay longer with them in the hospital, possibly to offer functional social support in this time of need.

In this study, number of individuals in the patient's household and martial status were two structural social support variables not associated with any other structural measure of social support. This finding suggests that the number of people a person relates to or has frequent contact with at home is not related to the size of their larger social network, the frequency of their participation in their social network, or the number of high contact social roles they take on. Although being married is one part of the calculation of the Social Network Index (SNI; Cohen et al., 1997), it appears to be independent of social network, social participation, and embedded network subscales derived from the SNI. Number of people living in one's household is another

structural measure of social support that should be clearly distinguished from Social Network Index subscale scores. Future research examining the impact of social integration and its components should consider the possibility that martial status and number of people in the household may be an independent or unique contributors to the construct of structural social support.

Relationship between functional and structural social support measures

Hypothesis 1 predicted that all three functional social support measures would be associated with all structural social support measures in this same of ACS patients within 2 days of hospitalization. This hypothesis was partially confirmed. The correlations between the number of hours the patient reported being accompanied by visitors during their hospitalization and all measures of functional social support (ISEL appraisal, ISEL belonging, and ISEL tangible), were moderate in size (rho's ranging from 0.33 to 0.40) and reached traditional significance levels. Furthermore, these relationships were predicted by Hypothesis 1, which permits a certain level of freedom from the constraints of the stringent Bonferroni-corrected alpha level. The more total time the patient receives visitors during their hospital stay, the higher the patient's perception of available functional social support. This finding lends support to the conclusion discussed above suggesting that high contact network members come to the hospital and stay longer in the hospital to offer tangible, instrumental, and emotional social support to the person suffering an ACS at this obvious time of need. The fact that the more tangible social support the patient reported, the lower his/her levels of subjective emotional distress caused by the hospitalization ($rho = -0.21$, $p < 0.05$) provides further evidence for this argument. An alternate explanation for

the relationship between hours visited and functional support measures is that the self-report variable number of hours accompanied during the hospital stay is biased by overall perceptions of functional social support. In other words, people who perceive functional social support to be highly available to them over-report the number of hours they actually spent with visitors to agree with their perceptions. Future studies should attempt to attain an objective measure of structural support, such as visitor's logs or direct observation of visitor-patient interaction, that are not influenced by self-report bias to help clarify this relationship between structural and functional social support measures.

In Hypothesis 1, we predicted that functional social support measures would be associated with other structural measures, including the Social Network Index variables. Such inter-relationships were not observed in the present study, in contrast to the findings of one of the few studies to examine inter-relationships in which social network was positively correlated with emotional and belonging social support, but not instrumental support (Seeman & Syme, 1987). The Seeman and Syme (1987) study was conducted in a sample of healthy individuals. One might expect that, in a sample of individuals under stress, such as patients hospitalized for ACS, these inter-relationships between structural and functional social support might be even stronger.

Accordingly, a sub-analysis of the present sample of ACS patients who reported being distressed at a level of 5 (midpoint of the 0-10 Likert scale) or higher was conducted to test the hypothesis that inter-relationships between structural and functional social support would be stronger in the high distress group. Within the 26 patients who reported average or higher distress caused by their hospitalization, ISEL functional support sub-scales were all positively correlated with SNI measures of social network at traditional levels of significance ($p < 0.05$).

Thus, it appears that a relationship between functional social support and various Social Network Index measures of structural social support only exists for these patients under times of perceived subjective stress. In the present study, a good portion of individuals did not report subjective distress due to their hospitalization, and this may have obscured finding significant inter-relationships between various structural and functional social support measures in the present sample.

Social support was associated with inflammatory markers in ACS patients

Social support may influence the development and progression of ACS via an association with inflammation. Thus, in Hypothesis 2a, we expected functional social support measures to be negatively associated with TNF-α, IL-6, and CRP levels in ACS patients. This hypothesis was partially confirmed. We found that the negative correlation between ISEL belonging and CRP and ISEL tangible and IL-6 were both moderate in size (rho = -0.32 and rho = -0.30, respectively) and reached traditional levels of significance ($p < 0.05$). As discussed previously, the fact that these relationships were hypothesized allows flexibility in the interpretation of significance in the context of a stringent Bonferroni-corrected alpha level. Furthermore, the magnitudes of these relationships and p values are impressive, given the small sample size in the present study. These findings are consistent with the literature indicating that emotional support is negatively correlated with percentage of monocytes (a marker of inflammation and precursor of the cytokine cascade) within two to four days of hospitalization for ACS (Gidron et al., 2003).

Functional social support and inflammation: Possible bio-behavioral pathways

The present study is unique in linking functional social support measures with inflammation as measured by the cytokine IL-6 and CRP, a systemic marker of inflammation further downstream, in cardiac patients. Social support may influence inflammatory markers through health behavior, medical/physiological, or psychological mechanisms. In this sample, functional social support levels were not associated with smoking or BMI, ruling out the health behavior pathway. Functional social support was also not associated with medical risk factors, such as hypertension, high cholesterol, diabetes, or having had a prior MI. These behavioral and medical pathways may be to be less likely to be activated during times of stress, such as the physiological stress on the body of having an ACS and the psychological stress of being hospitalized/aware of the severity of the physiological event that occurred. It is more likely that social support buffers the psychological consequences of an ACS (e.g., depression and anxiety, or a stress response), and thus impacts inflammatory markers. In this sample, rating of subjective emotional distress negatively and significantly correlated with perceived availability of tangible social support, as reported previously. Distress was also positively, but not significantly, correlated with IL-6 ($rho = 0.13$, $p = 0.39$) and CRP ($rho = 0.19$, $p = 0.22$) in this small sample.

It is possible that social support is influencing inflammatory levels through other psychological factors, such as depression, hopelessness, and anxiety. Tangible social support (one functional social support measure) was inversely associated with depression as measured on the BDI ($rho = -0.41$, $p < 0.01$) and state anxiety measured by the STAI ($rho = -0.40$, $p < 0.01$), while belonging social support (another functional social support measure) was inversely associated with depression assessed via the PHQ ($rho = -0.36$, $p < 0.05$) and the BDI (rho = -

0.53, $p < 0.001$). These relationships indicate that the more functional social support perceived to be available, the less depression and anxiety. Social support is associated with decreased stress in ACS patients within 2 days of hospitalization. However, in this sample, depression and state anxiety were not related to any inflammatory marker levels. Post-hoc analyses were conducted to test the buffering hypothesis. Interaction terms were created by multiplying either the tangible or belonging ISEL sub-scale scores by measures of distress, anxiety (STAI), or depression (BDI or PHQ). For IL-6, there was a marginally significant main effect for tangible social support ($\beta = -0.22$, $t = -1.79$, $p = 0.081$), and no main effect for BDI depression or interaction. For CRP, there was a main effect for belonging social support ($\beta = -0.31$, $t = -2.12$, $p < 0.05$), and no main effect for PHQ depression or interaction. There was a main effect for belonging social support ($\beta = -0.33$, $t = -2.89$, $p < 0.01$), a marginally significant main effect for BDI depression ($\beta = -0.11$, $t = -2.11$, $p = 0.056$), and no interaction on CRP. There was a main effect for belonging social support ($\beta = -0.31$, $t = -2.12$, $p < 0.05$), no main effect for distress, and a marginally significant distress x belonging support interaction ($\beta = 0.04$, $t = 1.74$, $p = 0.09$). These analyses suggest that social support does not buffer the effect of depression on inflammatory markers in this population, however the non-significant findings may be due to a lack power, or a limited ability to detect an interaction effect should one exist. These data and preliminary findings warrant further examination of the possibility that perceived functional social support may buffer and/or mediate the effects of distress/stress/depression on IL-6 and CRP levels.

Structural social support and inflammation: Possible bio-behavioral pathways

Contrary to Hypothesis 2a predicting that only functional social support measures would be associated with inflammatory markers, the correlations between specific structural measures of social support and certain inflammatory markers were also moderate in size and reached traditional levels of significance, despite a small sample size. For example, ACS patients who were married or living in a marital-like relationship had lower levels of IL-6 and TNF-α than those who were separated, divorced, widowed, or never married/living in a marital-like relationship ($p < 0.05$). Similarly, the number of people in the patient's household and IL-6 were inversely related ($p < 0.05$). This finding is especially interesting in light of previous research linking these particular structural social support constructs to poor outcomes in individuals post-MI. For example, Schmaltz and colleagues (2007) report that men living alone at the time of admission for MI had an increased risk of death over follow-up compared to those who were not, independent of other risk factors. Numerous studies from the literature also support the relationship between marital status and mortality and/or fatal/non-fatal cardiovascular events in individuals with CHD (e.g., Williams et al., 1992; Chandra 1983; Wiklund et al., 1988). In the present sample, these structural social support measures were not associated with any behavioral, medical, or psychological factor examined. Thus, the findings of the present study linking martial status to IL-6 and TNF-α and number of people in the household to IL-6 suggest that inflammation may be one pathway through which structural social support measures may impact prognosis in ACS patients, providing partial support for the model proposed in the introduction.

Post-hoc analyses conducted to test the buffering hypothesis for structural social support in this sample did not generally support a buffering effect, however due to possible power

problems, the findings are inconclusive. Interaction terms were created by multiplying either number of people in the household or marital status by measures of distress, anxiety (STAI), or depression (BDI or PHQ). For IL-6, there was a main effect for number of people in the household ($\beta = -0.41$, $t = -2.72$, $p < 0.01$), and no main effect for distress or interaction. There was a main effect for number of people in the household ($\beta = -1.11$, $t = -2.32$, $p < 0.05$), no main effect for anxiety, and a marginally significant anxiety x social support interaction ($\beta = 0.17$, $t = 1.04$, $p = 0.093$). Regarding the effects of marital status on IL-6, there was a main effect for marital status ($\beta = -1.59$, $t = -2.70$, $p < 0.01$) and no main effect for distress or interaction. There was a marginally significant main effect for marital status ($\beta = -0.87$, $t = -1.97$, $p = 0.056$), and no main effect for PHQ depression or interaction on IL-6. There was a main effect for marital status ($\beta = -01.12$, $t = -2.68$, $p < 0.05$), a marginally significant main effect for BDI depression ($\beta = -0.03$, $t = -1.84$, $p = 0.073$), and no interaction on IL-6. There was a main effect for marital status ($\beta = -2.40$, $t = -3.04$, $p < 0.01$), no main effect for anxiety, and an anxiety x marital status interaction ($\beta = 0.41$, $t = 2.28$, $p < 0.05$). For TNF-α, there was a main effect for marital status ($\beta = -0.76$, $t = -2.93$, $p < 0.01$), no main effect for PHQ depression and no interaction. There was also a main effect for marital status ($\beta = -0.73$, $t = -2.86$, $p < 0.01$), no main effect for BDI depression and no interaction. Taken together, structural support may buffer the effects of anxiety on IL-6 levels, but further research is needed to conclusively demonstrate a buffering effect of structural social on stress/depression/anxiety's relationship to inflammatory levels in this sample.

The relative strength of structural vs. functional social support measures on inflammation

Hypothesis 2b predicted that functional social support measures would predict inflammatory marker levels independent of structural social support measures. This hypothesis was not confirmed. In this sample of ACS patients, we found that number of people in the household predicted IL-6 levels within two days of hospitalization, independent of ISEL tangible social support and marital status. The mechanism for this relationship is not clear because, as discussed above, the number of people in the household was not associated with any behavioral, medical, or psychological factor studied. It is possible to propose a role for oxytocin, a hormone that has been associated with bonding and attachment in animals and humans, as playing a key role in social support's effect on inflammation. Research by the Karolinska Institute (1998), for example, indicates that daily ejections of the hormone decreased blood pressure and the stress hormone cortisol, and promoted weight gain and wound healing in male and female rats. The relationship between oxytocin and IL-6 has only been examined in the context of infection-mediated pre-term labor. Further research is needed to examine the mechanisms, such as oxytocin, through which structural (and functional) measures of social support might influence inflammation in healthy individuals in general and cardiac patients in particular.

Regarding the relative strength of functional and structural social support measures on TNF-α and CRP, marital status was the only significant correlate of TNF-α, while ISEL belonging social support was the only moderate correlate of CRP. It is interesting to note that functional and structural social support measures are the strongest predictors of different aspects of the cytokine cascade in ACS patients. Marital status was associated with the upstream cytokine TNF-α, which may have specific relevance for recurrent coronary events (Ridker et al.,

2000) and possibly heart failure because this cytokine mimics the HF phenotype when expressed at high concentrations (Seta et al., 1996). Number of people in the patient's household, another structural measure of social support, predicted IL-6, which is a more systemic, general marker of inflammation that is associated with cardiac problems as well as a variety of other diseases and conditions, including stress, cancer, rheumatoid arthritis, etc. Finally, belonging, a functional measure of social support, was associated with CRP levels. CRP is the downstream product of the cytokine cascade and is a low grade marker of general inflammation. These findings may suggest that structural social support measures has a stronger influence on inflammation on the upstream markers, while functional measures such as belonging intervene further downstream and affect CRP in patients recently hospitalized for ACS. Such an idea is novel and requires further study with larger, more diverse sample sizes in order to verify. The prospect of a social support hierarchy on inflammation in cardiac is intriguing nonetheless and warrants careful exploration.

Comparison of social support predictors of inflammatory marker levels

Hypothesis 3 predicted that ISEL belonging and ISEL appraisal functional social support measures would best predict TNF-α, IL-6, and CRP levels. This hypothesis was not confirmed. Backward linear regression analyses indicated that a combination of ISEL appraisal and the number of individuals in the patient's household was the strongest predictor of IL-6. As found in analyses for Specific Aim 2, backwards linear regression revealed marital status as the best predictor TNF-α. Backwards linear regression analysis for CRP resulted in none of the structural or functional social support variables being considered to be good predictors.

Although there are many criticisms of the backwards linear regression method, in Study II the approach has confirmed the value of marital status as a predictor of TNF-α levels within two days of hospitalization for ACS found in Specific Aim 2. It has also complicated the picture of predicting IL-6, revealing that appraisal and number of individuals in the patient's household are both equally important in determining IL-6 levels. Because these two social support variables are not correlated (rho = 0.00), functional and structural social support also unique contribute to inflammation as measured by IL-6 in this sample and are likely to work via different mechanisms. Future studies should examine the importance of both structural and functional forms of social support, or the quantity and quality of one's social relationships, and their bio-behavioral correlates to better understand how social support impacts inflammation in the hospital within 2 days of an ACS.

A possible role for loneliness?

Exploratory analyses were conducted to examine the relationship between loneliness and types of social support and its importance to inflammation in ACS. Results indicated that loneliness was negatively correlated with all three ISEL functional social support sub-scales (rho's ranged from -0.31 to -0.49) and none of the structural measures of social support. Given that the three questions used to define loneliness in this study appear to be tapping similar constructs as those measured by the ISEL. The UCLA Loneliness Scale asked patients (1) How often do you feel that you lack companionship? (2) How often do you feel left out? and (3) How often do you feel isolated from others? The ISEL belonging sub-scale asks about the perceived availability of people to do things with (e.g., go on a trip for a day, go to a movie, have lunch),

which is correlated with lacking companionship, and feeling isolated from others (to a lesser extent). The fourth item of the ISEL belonging sub-scale asks the degree to which the patient agrees with the statement "I don't often get invited to do things with others" which correlates with feeling left out. Because loneliness was moderately correlated with the other ISEL sub-scales as well, it seems clear that, in these data, the loneliness construct adds little to the perceived functional social support ISEL questionnaire. Furthermore, loneliness was not associated with inflammatory levels in this sample and does not appear to warrant investigation as a separate construct in cardiac patients hospitalized for ACS.

Potential limitations of Study II

Study II had several limitations, especially related to the sample, but these limitations were addressed in the study methodology or via further post-hoc analyses. For instance, patients received mediations during their hospital stay that may have affected inflammatory marker levels (e.g., aspirin). Analyses were re-run excluding individuals on NSAIDs other than aspirin (n = 6) and the results did not change, thus we can feel more confident that medication usage is not confounding the findings of the present study. Every attempt was made to identify and document comorbid inflammatory disorders (e.g., rheumatoid arthritis, cancer, etc.) in these ACS patients based on electronic medical record review. Analyses were re-run on individuals excluding patients with these disorders (n = 2) and the results did not change, suggesting that underlying inflammatory disease states are not influencing these results. Patients with cardiac symptoms due to cocaine/substance use were excluded from the study. Because approximately 5.5% of those meeting inclusion criteria were excluded due to cocaine use, it is unlikely that such a patient was

enrolled erroneously in Study II. The criteria for ACS allowed normal troponin levels, if the patient had chest pain or shortness of breath and EKG changes indicative of ischemia. Three participants had troponin levels < 0.06. The analyses were re-run on the sub-sample of patients with troponin levels greater than 0.06 and the results were similar, suggesting that our findings may generalize from the population of patients with ACS to the population of patients post-MI specifically.

Gender differences may have affected the results of Study II, so post-hoc analyses were conducted. Thirteen patients were female and analyses were re-run in the male sub-sample to test the proposed hypotheses. The relationships between functional and structural support tended to be stronger than in the overall sample, while the effect sizes describing the relationship between functional social support measures and immune function tended to be slightly smaller than those found in the sample as a whole. In the male sub-sample ($n = 33$), in addition to the relationship between number of people in the household and IL-6 ($r = -0.44$, $p < 0.01$), other structural social support variables were also associated with inflammatory markers, even though such relationships were not identified in the overall sample. For example, SNI sub-scale totals were associated with IL-6 and CRP. Total network size was negatively correlated with CRP ($r = -0.35$, $p < 0.05$), total network diversity was negatively correlated with IL-6 ($r = -0.49$, $p < 0.01$) and CRP ($r = -0.41$, $p < 0.05$), and number of embedded networks was also inversely associated with IL-6 ($r = -0.36$, $p < 0.05$) and CRP ($r = -0.36$, $p < 0.05$). These gender differences highlight the need for gender-specific analyses in studies examining the influence of social support on physiological markers. Unfortunately, the sample size of females was too small to test the proposed hypotheses. Presence of additional relationships between the two types of social

support suggest that poor structural social support is associated with inflammation in males only, possibly for the reasons described in the Study I discussion regarding the role of men as care receivers in social interactions and the conflict-free nature of their relationships.

In addition to potential sampling limitations, other extraneous variables could have affected the levels of inflammatory markers found in the blood of these patients, including time of blood draw, time until blood could be spun down in the centrifuge, and time until the serum could be placed in the freezer. Where possible, post-hoc analyses were conducted to account for these confounders. All blood was drawn before 12pm to account for circadian rhythms and the tubes were placed on ice immediately after the blood draw. IL-6, and possibly the other inflammatory markers measured, may have circadian variation that was explored in post-hoc analyses. Vgontzas and colleagues (2005) report that studies that have evaluated the 24-hour secretory pattern of IL-6 in healthy young adults suggest that IL-6 is secreted in a biphasic circadian pattern with two nadirs at about 08.00 and 21.00 and two zeniths at about 19.00 and 05.00 h. The distribution of the times blood was drawn indicated that 80% of the samples were taken between 10.00 and 12.00, while the other 20% were drawn between 7.00 and 10.00. Independent t-tests indicated that the levels of all three inflammatory markers were similar for those individuals who had their blood drawn in the earlier morning hours ($n = 9$) and those who had their blood drawn in the later morning hours ($n = 46$). These findings provide evidence to suggest that circadian variation is not affecting the relationships identified in the present study.

The time the serum was put in the freezer was documented, and the amount of time from blood draw until it could be frozen was calculated. Time-to-frozen was not correlated with IL-6 or TNF-α levels, but was found to be moderately correlated with CRP levels ($r = -0.33$, $p <$

0.05). The relationship between social support and CRP was re-examined, controlling for time-to-frozen, and there was no change in the findings. Thus, variability in the time to process the blood (as long as it was put on ice immediately after the draw), does not appear to account for the results of Study II.

The study has another methodological limitation that was addressed. Because all the functional and structural social support measures were self-report, they may have been biased by levels of emotional distress at the time of the interview. Emotional distress was inversely associated with ISEL tangible social support, but no other functional or structural social support variable. Furthermore, state anxiety (measured by the state portion of the STAI) was not associated with any measure of social support. Thus, although self-reported structural and functional social support levels do not seem to be influenced by emotional distress caused by the hospitalization or anxiety levels, individual biases may still be confounding the results of the present study.

One last limitation involves the representativeness of the sample. The final sample slightly under-represented females presenting with ACS at Bayview Hospital and under-represented the older individuals who present with ACS. Future studies should institute creative recruiting methods to ensure adequate participation of women and older patients during their hospitalization for ACS. Such techniques may involve involving family members in the consent process, spending additional time discussing with patients to address concerns, and obtaining the collaboration of the patient's doctor to explain the study and provide approval of participation in the study.

Integrative discussion

Study I and Study II had one common finding: functional and structural social support were found to be inversely associated with inflammatory levels as measured by IL-6 in males. Each study independently confirms the hypothesis that inflammation may be one mechanism through which social support can be health promoting, or through which lack of social support can exert a negative influence on health. Despite this hypothesis driven by the proposed model, IL-6 did not mediate the relationship found in Study I elderly males between lack of social integration and incident HF. Depression and self-reported rating of health compared to others were partial, but weak mediators of this relationship. Thus, the Study I findings suggest that, although lack of social integration is associated with the inflammatory marker IL-6, lack of social integration may work through psychological factors to impact the development of HF. The complimentary results of Study I and Study II linking social support to IL-6 in males, however, indicate that inflammation may be a bio-behavioral pathway worthy of examination in future studies of social support and the development and progression of cardiovascular disease.

There were two important differences between the findings of Study I and Study II: (1) differences in effect sizes, and (2) differences in the importance of psychological risk factors like depression. Study II sought to more closely examine the specific components of social support that might be associated with IL-6 and other inflammatory markers in a group of hospitalized ACS patients at risk for HF. In Study II, functional and structural social support measures were inversely associated with various markers of inflammation, including TNF-α, IL-6, and CRP. These relationships were stronger in males, as found in Study I, but the effect sizes for these relationships were much larger than those found in Study I (e.g., r's and rho's of 0.30 in Study II

vs. r's of 0.05 in Study I), despite Study II's small sample size. The Study II patients' heightened inflammatory states due to their ACS (Wasserman & Shipley, 2006) and their psychological stress associated with hospitalization (potentially affecting inflammatory levels) may account for the disparate findings. In other words, the baseline, or underlying, levels of inflammation were much different for the groups in each study.

A second difference in findings involves the role of depression. In Study I, depression was a partial mediator of the relationship between social integration and HF. In Study II, depression was not associated with structural social support or any inflammatory marker within the two days after ACS. The contrasting findings may be due to when depression was measured. In Study I, depression was a psychological risk score measured in a healthy, community-dwelling population and only 9.4% of the male sub-sample had CES-D scores ≥10, indicative of depressive symptoms. In Study II, on the other hand, depression was measured in a group studied with two days of an ACS. Approximately 26% (possible and probable mood disorder; PHQ ≥ 8) to 29% (mild, moderate, and severe depression; BDI ≥ 14) of patients in Study II presented depressive symptoms. These higher depression levels post-ACS may be more likely to reflect cardiac symptom status and/or possibly the severity of the event, whereas depression levels in a healthy population may be more likely to reflect a true psychological vulnerability. The findings from Study I or Study II do not provide evidence to support the buffering hypothesis. It seems that social support does not lessen the impact of depression on incident HF (in Study I) or inflammation (in Study II), although further examination of this mechanism may be warranted.

Implications for the conceptual model

The findings from Study I and Study II suggest that modification of the conceptual model proposed in the introduction may be necessary. First, gender differences in the relationship between social integration and HF highlight the importance of creating entirely separate models for males (see Figure 6) and females (see Figure 7). Second, in both male and female models, structural social support (as measured by social network size, network diversity, and embedded networks) and functional social support, surprisingly, were not highly correlated. The bi-directional arrow between structural and functional social support may be accurate when individuals are under stress, but not in general.

REVISED MODEL FOR MALES

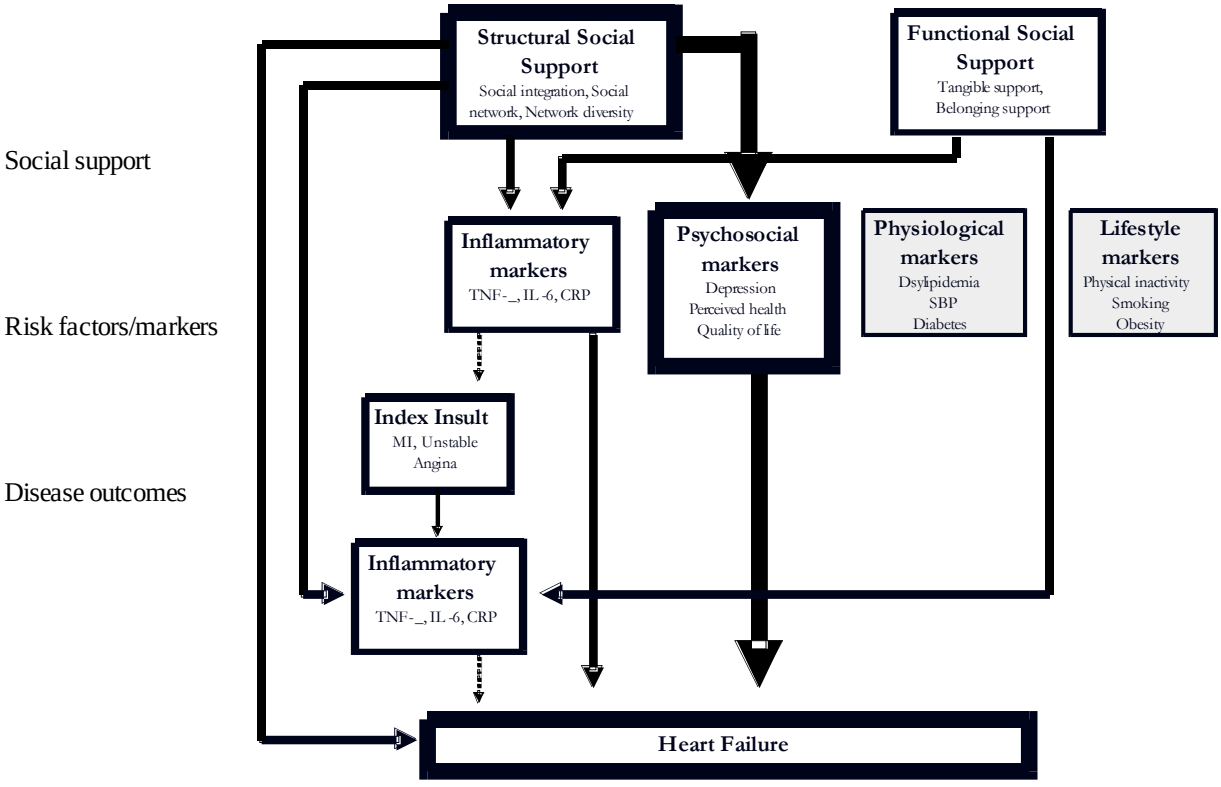

FIGURE 6: GENDER -SPECIFIC CONCEPTUAL MODEL - MALES

REVISED MODEL FOR FEMALES

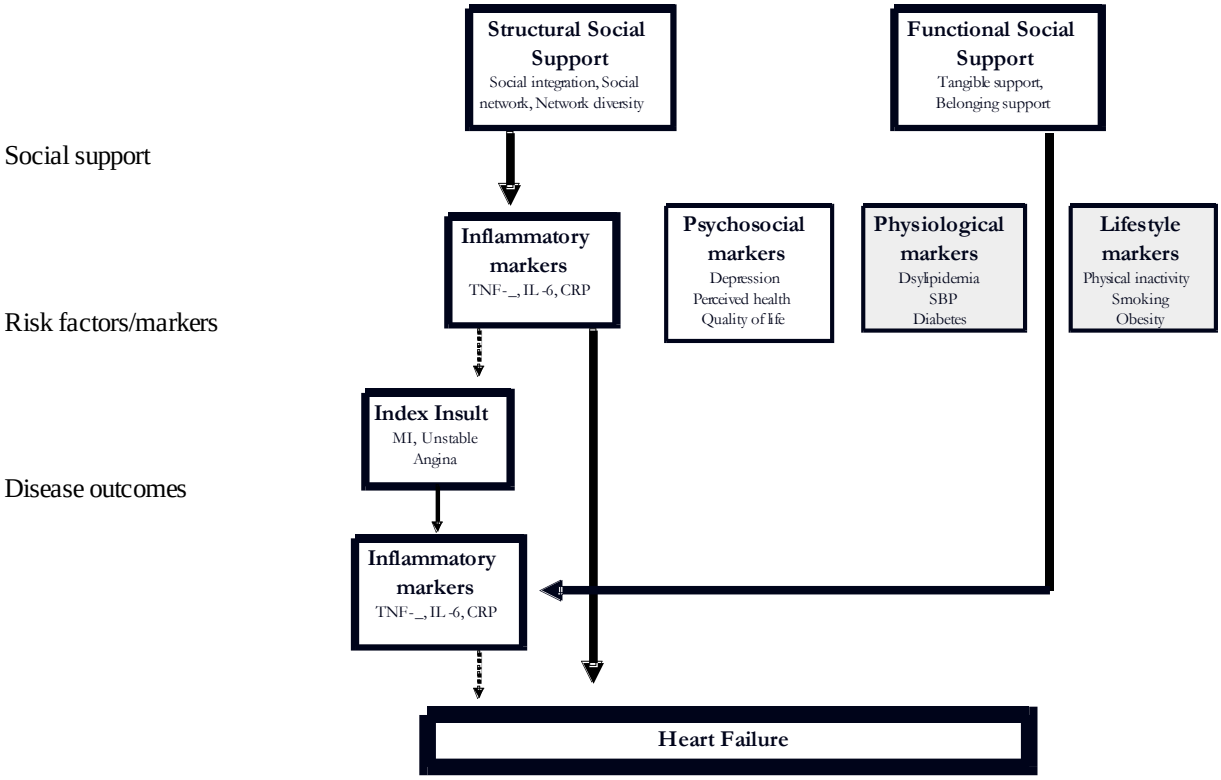

FIGURE 7: GENDER -SPECIFIC CONCEPTUAL MODEL - FEMALES

Causality can only be inferred regarding the relationship between social integration and incident HF in males in Study I. This relationship meets a number of Bradford Hill's criteria for causation, including: (1) a temporal relationship (the social integration score precedes heart failure onset); (2) strength of the relationship (the magnitude of the hazard ratios for social integration are similar to, and in some cases higher than, those for established, traditional HF risk factors; (3) a dose-response relationship (the magnitude decreases across social integration quartiles from lowest to highest with the highest quartile as the reference group); (4) plausibility (suggested by a psychosocial pathway mediating the relationship between poor social integration

and HF); and (5) coherence (the relationship between poor social integration and incident HF was predicted, guided by theory, and based on previous literature that associates structural social support with hard outcomes in CAD. The other Study I findings and Study II findings examining the relationship between social support and inflammatory markers were conducted using a cross-sectional study methodology. It is impossible to establish a temporal relationship between the variables of interest because they are measured simultaneously. However, establishing a priori hypotheses based on previous literature and in the context of a theoretical model (coherence and plausibility) can assist a social scientist in inferring cause from the data. Control of possible confounding variables, either through methodological design or statistical analyses after study completion, allow the consideration and ruling out of alternate explanations, another Bradford Hill criterion. Further research testing these relationship is recommended to establish consistency and build the argument of causation that social support contributes to inflammation and later adverse events in cardiac patients.

The findings of the present research, although not definitively because of their cross-sectional nature, indicate that the bio-behavioral pathways through which structural and functional social support each affect cardiovascular disease or cardiovascular disease processes are distinct and may differ by gender. The relationship between inflammatory markers and social support is stronger in males, and seems to be weaker or non-existent in females. Fourth, in a revised model for males, a psychosocial risk factor pathway linking and mediating social integration to HF must be added. Study I found that depression and self-reported health compared to others as partial mediators of the relationship between social integration in elderly males, providing evidence for psychosocial pathway mediation of the relationship. In contrast,

medical and lifestyle risk factor pathways were not supported by the results of the present studies.

Since Study II findings provide evidence for the inflammatory pathway in the proposed model, especially in males, inflammation is not ruled out entirely as an important player in the original model. However, according to the findings of the present research, inflammation may be more strongly related to both structural and functional social support after an index event than prior to the event. Thus, the fifth change to a revised model would potentially affect both male and female models and require the addition of an inflammatory pathway after ACS, possibly leading to future HF. This piece of the model would warrant further examination. Without a longitudinal follow-up of the Study II clinical sample, it is not known whether poor outcomes (and HF in particular) might be associated with elevated inflammatory levels observed within two days of an index event. Such models could provide assistance to researchers interested in investigating the bio-behavioral mechanisms linking social support to the development and progression of cardiovascular disease.

Future research

Given the relationship between lack of social integration and incident HF in males, additional large population-based studies of healthy and at-risk individuals are needed to delineate the specific aspects of lack of social integration (e.g., low number of social contacts, lack of participation in one's social network, the functional role of network members) that play an important role in the development and maintenance of HF. Structural and functional social support should be explored in detail, including received social support, conflict/satisfaction with

network relationships, and how well network members from different groups know each other, in order to better understand how social support may influence health. Similarly, objective measures of structural and functional social support ought to be obtained. Objective measures might include interviews with family and friends, observations of social interactions, diary writing from network members regarding their social relationship with other network members, or sign-in sheets at senior centers. Such objective assessments of social support might begin to validate the relationship found in Study I between the subjective impression of low social integration and incident HF in males.

Larger studies with healthy and at-risk populations examining bio-behavioral mechanisms of action of social support in the development and progression of CHD, MI, and HF are also needed. Inflammation is a one potential candidate mechanism with biological plausibility. This is supported by research suggesting that inflammation is important in the initiation of coronary plaques and the eventual disruption that contributes to thrombotic complications that occur in ACS and vulnerability to HF.

Since the evidence provided by Study II is based on cross-sectional methodology, longitudinal follow-up of a sample would allow a test of whether the higher inflammatory levels in these ACS patients, which were associated with functional or structural social support measures, predicted poorer cardiac outcomes (e.g., an MI, HF, or death). A prospective, longitudinal study of a sufficiently large sample is the only way to truly evaluate the importance of inflammation as a pathway that links social support to poor outcomes post-ACS. Study I findings also suggest that physiological mechanisms should not be the sole focus of investigation. Psychosocial factors such as depression and quality of life measures should also

receive considerable focus, especially in large-scale studies. Finally, health behaviors, especially adherence to treatment recommendations, deserves additional attention in population-based studies.

Practical/clinical implications

Following the epidemiological studies and smaller clinical research studies, research on effective primary, secondary, and tertiary social support interventions should also be encouraged. If the active components of social support that contribute to specific disease processes can be isolated, then targeted prevention programs can be developed and tested. Study I findings suggest that interventions to increase network size and/or participation are warranted to delay HF onset, and elderly males in particular should be targeted as an at-risk group. Social support networks can be strengthened through community activities, such as volunteering or religious involvement, and/or by reinforcing family ties. Study II findings indicate that structural and functional social support influences physiological state in ACS from the time of hospitalization. Outreach to individuals with CAD and their family and friends might help this network to activate at the time of need. Primary and secondary prevention in the area of social support (e.g., how to develop and maintain supportive relationships, how to build and continue a successful marriage, how to reach out for support from friends and family, how to help friends or family in times of need) may be beneficial for the general population, individuals with CAD risk factors, and individuals with documented CAD. Males may be especially likely to benefit from these intervention programs, and attention to their specific social needs are warranted.

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Appendix A

Questionnaires Administered in Study II

Hopelessness Study: Platelet - Demographic Data

Date:_____ Participant #_____ Time of Blood Draw: _____

1. Name:_____Code:_____
2. Date of Birth:_____(MM/DD/YYYY) MRN:_____
3. Gender: M / F 3a. Race:_____ 3b. Age_____
4. Date of arrival:_____ 4a. Date of study enrollment:_____
5. Presenting complaints: _____

_____

6. Current primary diagnosis: _____

   6a. If MI, ST-segment elevation present: Y / N

   6b. If MI, ejection fraction: _____

   6c. If MI, peak Troponin:_____
7. Secondary diagnoses: _____
8. Hypertension: Y / N (BP≥ 140/90 or on treatment for hypertension)
9. Family History: Men < 55: Y / N Women< 65: Y / N
10. Current Smoker: Y / N
11. Past Smoker: Y / N Date stopped:_____
12. Hypercholesterolemia (LDL > 130, total chol. > 220): Y / N
13. Diabetes: Y / N
14. CAD: Y / N
15. Prior MI: Y / N Date: _____Date: _____Date:_____
16. BMI: _____ Alternately, Weight: _____ Height: _____

17. Medications:

Notes:

Phone #:

Address:

ISEL-12

Instructions: This scale is made up of a list of statements each of which may or may not be true about you. For each statement circle "definitely true" if you are sure it is true about you and "probably true" if you think it is true but are not absolutely certain. Similarly, you should circle "definitely false" if you are sure the statement is false and "probably false" if you think it is false but are not absolutely certain.

1. If I wanted to go on a trip for a day (for example, to the country or mountains), I would have a hard time finding someone to go with me.

1. definitely false 2. probably false 3. probably true 4. definitely true

2. I feel that there is no one I can share my most private worries and fears with.

1. definitely false 2. probably false 3. probably true 4. definitely true

3. If I were sick, I could easily find someone to help me with my daily chores.

1. definitely false 2. probably false 3. probably true 4. definitely true

4. There is someone I can turn to for advice about handling problems with my family.

1. definitely false 2. probably false 3. probably true 4. definitely true

5. If I decide one afternoon that I would like to go to a movie that evening, I could easily find someone to go with me.

1. definitely false 2. probably false 3. probably true 4. definitely true

6. When I need suggestions on how to deal with a personal problem, I know someone I can turn to.

1. definitely false 2. probably false 3. probably true 4. definitely true

7. I don't often get invited to do things with others.

1. definitely false 2. probably false 3. probably true 4. definitely true

8. If I had to go out of town for a few weeks, it would be difficult to find someone who would look after my house or apartment (the plants, pets, garden, etc.).

1. definitely false 2. probably false 3. probably true 4. definitely true

9. If I wanted to have lunch with someone, I could easily find someone to join me.

1. definitely false 2. probably false 3. probably true 4. definitely true

10. If I was stranded 10 miles from home, there is someone I could call who could come and get me.

1. definitely false 2. probably false 3. probably true 4. definitely true

11. If a family crisis arose, it would be difficult to find someone who could give me good advice about how to handle it.

1. definitely false 2. probably false 3. probably true 4. definitely true

12. If I needed some help in moving to a new house or apartment, I would have a hard time finding someone to help me.

1. definitely false 2. probably false 3. probably true 4. definitely true

Social Network Index

Instructions: This questionnaire is concerned with how many people you see or talk to on a regular basis including family, friends, workmates, neighbors, etc. Please read and answer each question carefully. Answer follow-up questions where appropriate.

1. Which of the following best describes your marital status?
____ (1) currently married & living together, or living with someone in marital-like relationship
____ (2) never married & never lived with someone in a marital-like relationship
____ (3) separated
____ (4) divorced or formerly lived with someone in a marital-like relationship
____ (5) widowed

2. Who do you live with (indicate the person's relationship to you): _____

_____

3. Who has come to see you in the hospital so far (indicate the person's relationship to you)? How long has each person stayed with you here in the hospital in total?

_____

_____

_____

4. How many children do you have? (If > 0, answer 4a.)
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

4a. How many of your children do you see/talk to on the phone at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

5. Are either of your parents living? (If yes, answer 5a.)
____ (0) neither ____ (1) mother only
____ (2) father only ____ (3) both

5a. Do you see or talk on the phone to either of your parents at least once every 2 weeks?
____ (0) neither ____ (1) mother only
____ (2) father only ____ (3) both

6. Are either of your in-laws/partner's parents living? (If yes, answer 6a.)
____ (0) neither ____ (1) mother
____ (2) father ____ (3) both ____ (4) N/A

6a. Do you see or talk on the phone to either of your in-laws at least once every 2 weeks?
_____ (0) neither _____ (1) mother only
_____ (2) father only ____ (3) both

7. How many other relatives (other than your spouse, parents & children) do you feel close to? (If > 0, answer 7a.)
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

7a. How many of these relatives do you see or talk to on the phone at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

8. How many close friends do you have? (meaning people that you feel at ease with, can talk to about private matters, and can call on for help) (If > 0, answer 8a.)
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

8a. How many of these friends do you see or talk to at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

9. Do you belong to a church, temple, or other religious group? (If yes, answer 9a.)
_____ no _____ yes

9a. How many members of your church or religious group do you talk to at least once every 2 weeks? (This includes at group meetings and services.)
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

10. Do you attend any classes (school, university, technical training, or adult education) on a regular basis? (If yes, answer 10a.)
_____ no _____ yes

10a. How many fellow students or teachers do you talk to at least once every 2 weeks? (This includes at class meetings.)
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

11. Are you currently employed either full or part-time? (If yes, answer 11a and 11b.)
_____ (0) no
_____ (1) yes, self-employed
_____ (2) yes, employed by others

11a. How many people do you supervise?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

11b. How many people at work (other than those you supervise) do you talk to at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

12. Which best describes the place where you live? (Answer 12a.)
_____ Individually detached house
_____ Townhouse or duplex
_____ Apartment
_____ Assisted living apartment
_____ Nursing home
_____ Other:

12a. How many of your neighbors do you visit or talk to at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

13. Are you currently involved in regular volunteer work? (If yes, answer 13a.)
_____ no _____ yes

13a. How many people involved in this volunteer work do you talk to about volunteering-related issues at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

14. Do you have any regular visits with professionals (doctors, nurses, home health aids, cleaning help, etc.) at least once every two weeks? (If yes, answer 12a.)
_____ no _____ yes

14a. How many people do you see or have appointments with on a regular basis at least once every 2 weeks?
____0 ____1 ____2 ____3
____4 ____5 ____6 ____7 or more

15. Do you belong to any groups in which you talk to one or more members of the group about group-related issues at least once every 2 weeks? Examples include social clubs, recreational groups, trade unions, commercial groups, professional organizations, groups concerned with children like the PTA or Boy Scouts, groups concerned with community service, etc. (If yes, answer 15a; if no, end of questionnaire.)
_____ no _____ yes

15a. Consider those groups in which you talk to a fellow group member at least once every 2 weeks. Please provide the following information for each such group: the name or type of group and the total number of members in that group that you talk to at least once every 2 weeks.

Group that you talk to at least once every 2 weeks	Total number of group members
1.	
2.	
3.	
4.	

This scale was adapted from the scale printed in the following journal article:

Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S., and Gwaltney, J. M. Jr. (1997). Social ties and susceptibility to the common cold. Journal of the American Medical Association, 277, 1940-1944. Link to full-text (pdf)

R-UCLA Loneliness Scale – 3 Items

From Russell, Peplau, and Cutrona, 1980

The next questions are about how you feel about different aspects of your life. For each one, tell me how often you feel that way.

Lead in and questions are read to the respondent.	HE	ST	O
1. How often do you feel that you lack companionship: Hardly ever, some of the time, or often?	1	2	3
2. How often do you feel left out: Hardly ever, some of the time, or often?	1	2	3
3. How often do you feel isolated from others: Hardly ever, some of the time, or often?	1	2	3

How much emotional distress has this hospitalization caused you on a scale from 0 – 10, with 0 representing no distress and 10 representing maximum distress?

_____

SELF-EVALUATION QUESTIONNAIRE

Developed by Charles D. Spielberger
in collaboration with
R. L. Gorsuch, R. Lushene, P. R. Vagg, and G. A. Jacobs

STAI Form Y-1

Name _____ Date _____ S ____

Age _____ Sex: M ____ F ____ T ____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	①	②	③	④
2. I feel secure	①	②	③	④
3. I am tense	①	②	③	④
4. I feel strained	①	②	③	④
5. I feel at ease	①	②	③	④
6. I feel upset	①	②	③	④
7. I am presently worrying over possible misfortunes	①	②	③	④
8. I feel satisfied	①	②	③	④
9. I feel frightened	①	②	③	④
10. I feel comfortable	①	②	③	④
11. I feel self-confident	①	②	③	④
12. I feel nervous	①	②	③	④
13. I am jittery	①	②	③	④
14. I feel indecisive	①	②	③	④
15. I am relaxed	①	②	③	④
16. I feel content	①	②	③	④
17. I am worried	①	②	③	④
18. I feel confused	①	②	③	④
19. I feel steady	①	②	③	④
20. I feel pleasant	①	②	③	④

Consulting Psychologists Press, Inc.
3803 E. Bayshore Road • Palo Alto, CA 94303

Beck Depression Inventory -Second Edition

BDI-II

Date:_____

Name:_____ Marital Status:_____

Age: ____ Sex:____ Occupation: _____ Education:_____

Inst ructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including tod ay**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1.
0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2.
0 I am not discouraged about my future.
1 I feel more d iscouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3.
0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4.
0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any p leasure from the things I used to enjoy.

5.
0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.
0 I don't feel I am bei ng punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.
0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8.
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9.
0 I don't have any thoughts of killing myself.
1 I have thoughts of k illing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11.

0 I am no more restless or would up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12.

0 I have n ot lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13.

0 I make decision s about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14.

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15.

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16.

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1 -2 hours early and can't get back to sleep.

17.

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18.

0 I h ave not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19.

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20.

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Beck Hopelessness Scale

1	I look forward to the future with hope and enthusiasm.	**True**	**False**
2	I might as well give up because I can't make things better for myself.	**True**	**False**
3	When things are going badly, I am helped by knowing they can't stay that way forever.	**True**	**False**
4	I can't imagine what my life would be like in 10 years.	**True**	**False**
5	I have enough time to accomplish the things I most want to do.	**True**	**False**
6	In the future, I expect to succeed in what concerns me most.	**True**	**False**
7	My future seems dark to me.	**True**	**False**
8	I expect to get more of the good things in life than the average person.	**True**	**False**
9	I just don't get the breaks, and there's no reason to believe I will in the future.	**True**	**False**
10	My past experiences have prepared me well for my future.	**True**	**False**
11	All I can see ahead of me is unpleasantness rather than pleasantness.	**True**	**False**
12	I don't expect to get what I really want.	**True**	**False**
13	When I look ahead to the future, I expect I will be happier than I am now.	**True**	**False**
14	Things just won't work out the way I want them to.	**True**	**False**
15	I have great faith in the future.	**True**	**False**
16	I never get what I want so it's foolish to want anything.	**True**	**False**
17	It is very unlikely that I will get any real satisfaction in the future.	**True**	**False**
18	The future seems vague and uncertain to me.	**True**	**False**
19	I can look forward to more good times than bad times.	**True**	**False**
20	There's no use in really trying to get something I want because I probably won't get it.	**True**	**False**

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ **DATE:** _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
	add columns:	+	+	
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card.)	**TOTAL:**			

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- **Not difficult at all** _____
- **Somewhat difficult** _____
- **Very difficult** _____
- **Extremely difficult** _____

Appendix B

Johns Hopkins University Institutional Review Board
approval letter for originally proposed study

JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE
Website http://irb.jhmi.edu

Office of Human Subjects Research
Institutional Review Boards

1620 McElderry Street / Reed Hall, Suite 1300 B
Baltimore, MD 21205-2011
(410) 955-3008
(410) 955-0867 Fax
E-mail: jhmirb@jhmi.edu

JHM-IRB X

INITIAL APPLICATION APPROVAL NOTICE CONVENED REVIEW With Consent Form

TO : Marlene Williams
Assistant Professor, Cardiology
JHBMC

FROM: Peter Terry, MD
Acting Chairman - JHM-IRB X

DATE: November 13, 2006

RE : **Application Number: NA_00005510, entitled, The Relationship of Depression and Hopelessness to Platelet Activation Following Acute Myocardial Infarction (with David Bush, James Fauerbach, Gina Magyar-Russell, Una McCann, Roy Ziegelstein)**

I am pleased to inform you that at the convened meeting of **11/09/2006** the **JHM-IRB X** voted to approve the above-referenced application. Approval of the research is for the period of **11/09/2006 to 11/08/2007.** As principal investigator of the research, you are responsible for fulfilling the following requirements of approval:

1) The co-investigators listed on the application should be kept informed of the status of the research.
2) Submit a Further Study Action (FSA) in eIRB for any changes in research. These changes in research are required to be reviewed and approved prior to the activation of the changes, with the following exception: changes made to eliminate an apparent immediate hazard to the research participant may be instituted immediately and the JHM IRB should be informed of such changes promptly in eIRB.
3) Unanticipated problems involving risks to participants or others must be reported to the JHM IRB in accord with the **JHM IRB Organization Policy on Reports of Unanticipated Problems Involving Risks to Participants or Others (Policy No. 103.6(b).** Submit an FSA – Problem/Event in eIRB.
4) Only consent forms with a valid approval stamp may be presented to participants. All consent forms signed by subjects enrolled in the study should be retained on file. The Office of Human Subjects Research conducts periodic compliance monitoring of protocol records, and consent documentation is part of such monitoring.
5) Federal regulations require review of approved research not less than once per year. **Therefore, a continuing review application must be submitted as an FSA in eIRB no later than six weeks prior to the expiration date of 11/08/2007. This will allow sufficient time for review of the application to be completed prior to the expiration date.** Failure to submit a continuing review application prior to the expiration date will result in termination of the research, at which point new participants may not be enrolled and currently enrolled participants must discontinue participation in the study.

PT: emead1

Enclosure

Appendix C

Johns Hopkins University Institutional Review Board
approval letter for amended study, including protocol proposed in Study II

JOHNS HOPKINS
MEDICINE
SCHOOL OF MEDICINE
Website http://irb.jhmi.edu

Office of Human Subjects Research
Institutional Review Boards

1620 McElderry Street / Reed Hall, Suite B130
Baltimore, MD 21205-2011
(410) 955-3008
(410) 955-0867 Fax
E-mail: jhmirb@jhmi.edu

JHM-IRB X

INITIAL APPLICATION APPROVAL NOTICE CONVENED REVIEW With Consent Form

TO : Marlene Williams
Assistant Professor, Cardiology
JHBMC

FROM: Peter Terry, MD
Acting Chairman - JHM-IRB X

DATE: November 13, 2006

RE : **Application Number: NA_00005510, entitled, The Relationship of Depression and Hopelessness to Platelet Activation Following Acute Myocardial Infarction (with David Bush, James Fauerbach, Gina Magyar-Russell, Una McCann, Roy Ziegelstein)**

I am pleased to inform you that at the convened meeting of **11/09/2006** the **JHM-IRB X** voted to approve the above-referenced application. Approval of the research is for the period of **11/09/2006 to 11/08/2007.** As principal investigator of the research, you are responsible for fulfilling the following requirements of approval:

1) The co-investigators listed on the application should be kept informed of the status of the research.
2) Submit a Further Study Action (FSA) in eIRB for any changes in research. These changes in research are required to be reviewed and approved prior to the activation of the changes, with the following exception: changes made to eliminate an apparent immediate hazard to the research participant may be instituted immediately and the JHM IRB should be informed of such changes promptly in eIRB.
3) Unanticipated problems involving risks to participants or others must be reported to the JHM IRB in accord with the **JHM IRB Organization Policy on Reports of Unanticipated Problems Involving Risks to Participants or Others (Policy No. 103.6(b).** Submit an FSA – Problem/Event in eIRB.
4) Only consent forms with a valid approval stamp may be presented to participants. All consent forms signed by subjects enrolled in the study should be retained on file. The Office of Human Subjects Research conducts periodic compliance monitoring of protocol records, and consent documentation is part of such monitoring.
5) Federal regulations require review of approved research not less than once per year. **Therefore, a continuing review application must be submitted as an FSA in eIRB no later than six weeks prior to the expiration date of 11/08/2007. This will allow sufficient time for review of the application to be completed prior to the expiration date.** Failure to submit a continuing review application prior to the expiration date will result in termination of the research, at which point new participants may not be enrolled and currently enrolled participants must discontinue participation in the study.

PT: emead1

Enclosure

Appendix D

Johns Hopkins University Institutional Review Board
approved consent form for amended study

JOHNS HOPKINS MEDICINE

Approval Expires November 8, 2007

Sites of Research:
The Johns Hopkins Bayview Medical Center

Patient I.D. Plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: The relationship of depression and hopelessness to platelet activation following acute myocardial infarction

Application No.: NA_00005510

Sponsor: National Institutes of Health

Principal Investigator: Dr. Marlene Williams

Date: March 13, 2007

1. What you should know about this study:

- You are being asked to join a research study.
- This consent form explains the research study and your part in the study.
- Please read it carefully and take as much time as you need.
- Please ask questions at any time about anything you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. You can decide not to take part or you can quit at any time. There will be no penalty or loss of benefits if you decide to quit the study.
- We may learn things during the study that might make you want to stop being in the study. If this happens, we will tell you about it. You can then decide if you want to stay in the study.

2. Why is this research being done?

Previous research studies show that people who are sad or "blue" after they have a heart attack do not do as well as others. It is not yet known why this is the case. This research study is being done to find out whether people who are sad or "blue" after a heart attack are more likely to form blood clots than others. We also hope to learn whether people who feel hopeless after a heart attack are more likely to form blood clots than others. Finally, we are interested in finding out how interactions with and help from family and friends might affect your body's ability to form clots and its immune system response to a heart attack. About 60 people will be asked to join this study.

3. What will happen if you join this study?

If you agree to join this study, we will collect about 6 teaspoons of blood from a vein in your arm. This will be done while you are a patient at Johns Hopkins Bayview Medical Center. We will also ask you to complete several paper-and-pencil forms that tell us how you are feeling and about the frequency of your interactions with family and friends.

4. What are the risks or discomforts of the study?

Taking blood carries some risks. A needle is placed in a vein for a short time, and that can cause some mild pain. Sometimes, a bruise will occur where the needle is placed in the skin. Putting a needle in the skin may also cause bleeding. It is possible that an infection could occur. We do not expect this to happen.

Paper and pencil forms may make you feel nervous. This is more likely if you are sick, weak or have trouble answering the questions. This is not expected last very long.

You can choose to not answer any question(s) if you wish.

5. Are there benefits to being in the study?

You will not benefit personally by being in this research study. We hope that the things we learn as a result of this study will help other people with heart attacks who are sad or "blue."

6. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

7. Will it cost you anything to be in this study?

The study procedures will be provided at no cost to you.

8. Will you be paid if you join this study?

You will not be paid if you join this study.

9. Can you leave the study early?

You may leave the study at any time. If you wish to leave the study, please let the study staff know right away. If you leave the study, your care at Johns Hopkins Bayview Medical Center will not be affected.

10. Why might we take you out of the study early?

Your participation in this research study may be ended without your consent. You will not be in the study if we cannot collect a blood sample or if you cannot complete the paper-and-pencil forms.

11. How will your privacy be protected?

Johns Hopkins has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

Generally, only people on the research team will know that you are in the research study and will see your information. However, there are a few exceptions that are listed later in this section of the consent form.

The people working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details.

The research team will need to see your information. Sometimes other people at Johns Hopkins may see or give out your information. These include people who review the research studies, their staff, lawyers,

People outside of Johns Hopkins may need to see your information for this study. Examples include government groups (such as the Food and Drug Administration), safety monitors, other hospitals in the study and companies that sponsor the study.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Hopkins who receive your information may not be covered by this promise. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The use of your information has no time limit. You can cancel your permission to use and disclose your information at any time by calling the Johns Hopkins Medicine IRB at 410-955-3008 or by sending a letter to:

Office of Human Subjects Research
1620 McElderry Street
Reed Hall, Suite B130
Baltimore, MD 21205-1911

Your cancellation would not affect information already collected in this study.

12. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?
The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other concerns or questions about the research.

b. What do you do if you have questions about the study?
Call the doctor responsible for this study, Dr. Marlene Williams at 410-550-7040. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?
If you have an urgent medical problem related to your being in this study, call Dr. Marlene Williams at 410-550-7040.

If you think you are injured or ill as a result of being in this study, call the doctor responsible, Dr.

Medical care at Johns Hopkins is open to you as it is to all sick or injured people. Johns Hopkins does not have a program to pay you if you are hurt or have other bad results from being in the study. The costs for any treatment or hospital care would be charged to you or your insurance company.

d. What happens to Data, Tissue, Blood and Samples that are collected in the study?

Scientists at Johns Hopkins work to find the causes and cures of disease. The data, tissue, blood and samples collected from you during this study are important to both this study and to future research.

If you join this study:

- Johns Hopkins and/or its outside partners in this research will own these data, tissue, blood and samples.
- Scientists may only use materials or data that identify you for future research with your consent or IRB approval.
- If this material is used to create a product or idea, the scientists and Johns Hopkins will own that product or idea.
- You will not receive any financial benefit from the creation, use or sale of that product or idea.

e. What are the organizations that are part of Johns Hopkins?

Johns Hopkins includes the following:

- The Johns Hopkins University
- The Johns Hopkins Hospital
- Johns Hopkins Bayview Medical Center
- Howard County General Hospital
- Johns Hopkins Community Physicians.

13. What does your signature on this consent form mean?

Your signature on this form means that:

- you understand the information given to you in this form
- you accept the provisions in the form
- you agree to join the study

You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

This consent form is approved from 03/13/2007 to 11/08/2007.

Do not sign after the expiration date of: 11/08/2007

_____

Signature of Participant Date

_____

Signature of Person Obtaining Consent Date

_____

Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required) Date

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND, IF APPROPRIATE A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD.

FOR OFFICE USE ONLY:
STUDY APPROVED FOR ENROLLMENT OF: _X_ **Adults Only** ___ Adults and Children ___ Children Only

Appendix E

Uniformed Services University of the Health Sciences

Institutional Review Board approval letter for proposed Study I and Study II